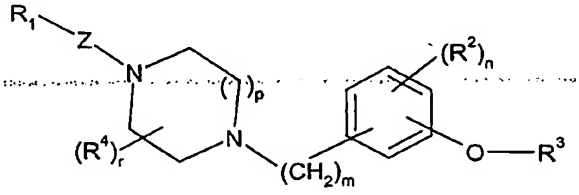
SUBSTITUTED PIPERAZINES, (1,4)DIAZEPINES, AND 2,5-DIAZABICYCLO(2.2.1)HEPTANES AS HISTAMINE H1 AND/OR H3 ANTAGONISTS OR HISTAMINE H3 REVERSE ANTAGONISTS

The present invention relates to novel piperazine and azepine derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurodegenerative disorders including Alzheimer's disease.

WO 02/76925 (Eli Lilly) describes a series of compounds which are claimed to be histamine H3 antagonists. WO 02/055496 (GlaxoSmithKline) describes a series of piperidine and piperazine derivatives which are claimed to be inducers of LDL-receptor expression. WO 02/12214 (Ortho McNeil Pharmaceutical Inc) describes a series of substituted aryloxyalkylamines which are claimed to be histamine H3 antagonists.

The histamine H3 receptor is expressed in both the mammalian central nervous system (CNS), and in peripheral tissues (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic, adrenergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H3 antagonists and/or inverse agonists such as the current series could be useful for the treatment of cognitive impairments in neurological diseases such as Alzheimer's disease and related neurodegenerative disorders.

The present invention provides, in a first aspect, a compound of formula (I):



(I)

wherein:

R^1 represents hydrogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-

heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl,- heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl, -heterocyclyl-heterocyclyl,

wherein R^1 may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, $COOR^{15}$, cyano, -C_{1-6} alkyl-cyano, nitro, oxo, trifluoromethyl, trifluoromethoxy, fluoromethoxy, difluoromethoxy, C_{1-6} alkyl (optionally substituted by a $COOR^{15}$ group), C_{2-6} alkenyl (optionally substituted by a $COOR^{15}$ group), C_{2-6} alkynyl (optionally substituted by a $COOR^{15}$ group), C_{1-6} alkoxy (optionally substituted by a $COOR^{15}$ group), pentafluoroethyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, aryl, arylC_{1-6} alkyl, -CO-aryl (optionally substituted by a halogen atom), -CO-heteroaryl, -C_{1-6} alkyl-CO-aryl, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group -COR^{15}, -$NR^{15}R^{16}$, -$CONR^{15}R^{16}$, -$NR^{15}COR^{16}$, -$NR^{15}SO_2R^{16}$ or -$SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl or together may be fused to form a 5- to 7- membered non-aromatic heterocyclic ring optionally interrupted by an O or S atom and optionally substituted by a halogen, C_{1-6} alkyl or -C_{1-6} alkylC_{1-6} alkoxy group;

Z represents a bond, CO, $N(R^{10})CO$ or SO_2, such that when R^1 represents hydrogen, Z represents $NR^{10}CO$;

p is 1 or 2;

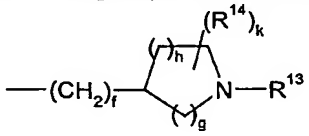
m, n and r independently represent 0, 1 or 2;

R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl, such that when n represents 2, two R^2 groups may instead be linked to form a phenyl ring;

R^4 represents C_{1-6} alkyl, or when r represents 2, two R^4 groups may instead together form a bridged CH_2, $(CH_2)_2$ or $(CH_2)_3$ group;

R^{10} represents hydrogen or C_{1-6} alkyl, or R^{10}, together with the nitrogen to which it is attached and R^1 forms a nitrogen containing heterocyclic group;

R^3 represents -$(CH_2)_q$-$NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;

R^{11} and R^{12} independently represent C_{1-6} alkyl or C_{3-8} cycloalkyl or together with the nitrogen atom to which they are attached represent an N-linked nitrogen containing heterocyclyl group optionally substituted by one or more R^{17} groups;

R^{13} represents hydrogen, C_{1-6} alkyl, -C_{1-6} alkyl-C_{1-6} alkoxy, C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl or heterocyclyl;
R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloalkyl, OH, diC_{1-6} alkylamino, C_{1-6} alkoxy or heterocyclyl;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
with the proviso that when m represents 1, n and r both represent 0 and R^3 represents –$(CH_2)_3$-N-piperidine or –$(CH_2)_3$-N(ethyl)$_2$, R^1-Z represents a group other than methyl, -CO-O-C$(CH_3)_3$ or benzyl;
and with the proviso that when m, n and r all represent 0, p represents 1, R^3 represents –$(CH_2)_3$-N-pyrrolidine or –$(CH_2)_3$-N-piperidine, R^1 represents benzyl, Z represents a group other than a bond;
and with the proviso that when m, n and r all represent 0, p represents 1, R^3 represents–$(CH_2)_3$-N-piperidine, R^1 represents isopropyl, Z represents a group other than a bond;
and with the proviso that when m represents 1, n and r both represent 0, p represents 1, R^3 represents–$(CH_2)_3$-N-piperidine, R^1 represents methyl, isopropyl, aryl or benzyl, Z represents a group other than a bond;
and with the proviso that when m and n both represent 0, R^3 represents –$(CH_2)_3$-N(ethyl)$_2$, p represents 1, r represents 2 and R^1 and R^4 both represent methyl, Z represents a group other than a bond;
or a pharmaceutically acceptable salt thereof.

In one particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein:
R^1 represents a group other than hydrogen, -C_{1-6} alkoxy or -C_{1-6} alkyl-C_{3-8} cycloalkyl; and R^1 is optionally substituted by one or more substituents other than $COOR^{15}$, -C_{1-6} alkyl-cyano, C_{1-6} alkyl substituted by a $COOR^{15}$ group), C_{2-6} alkenyl (optionally substituted by a $COOR^{15}$ group), C_{2-6} alkynyl (optionally substituted by a $COOR^{15}$ group), C_{1-6} alkoxy (optionally substituted by a $COOR^{15}$ group), C_{2-6} alkenoxy, aryl, arylC_{1-6} alkyl, -CO-aryl (optionally substituted by a halogen atom), -CO-heteroaryl, -C_{1-6} alkyl-CO-aryl or C_{3-7} cycloalkyl; and
R^{15} and R^{16} independently represent a group other than C_{3-8} cycloalkyl or together may be fused to form an unsubstituted 5- to 7- membered non-aromatic heterocyclic ring optionally interrupted by an O or S atom; and
r represents 0; and
two R^2 groups are not linked to form a phenyl ring; and
R^{11} and R^{12} independently represent a group other than C_{3-8} cycloalkyl; and
R^{13} represents a group other than -C_{1-6} alkyl-C_{3-8} cycloalkyl.

In a second particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein m represents 0 or 2.

In a further particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein Z represents CO, $CONR^{10}$ or SO_2.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes single and fused rings wherein at least one ring is aromatic, for example, phenyl, naphthyl, tetrahydronaphthalenyl, indanyl or fluorenyl.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated ring or a 4-7 membered saturated or partially unsaturated ring fused to a benzene ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, diazepanyl, azepanyl and azocanyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, benzodioxolyl and dihydroisoquinolinyl.

The term "nitrogen containing heterocyclyl" is intended to represent any heterocyclyl group as defined above which contains a nitrogen atom.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include furopyridinyl and benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive dysfunction, epilepsy, neuropathic pain, inflammatory pain, migraine, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy, psychiatric disorders including schizophrenia, attention deficit hyperactivity disorder, depression and addiction; and other diseases including obesity, asthma,

alkenyl (eg. ethenyl) optionally substituted by $COOR^{15}$ (eg. COOMe); C_{3-7} cycloalkyl (eg. cyclopentyl); C_{1-6} alkylsulfonyl (eg. $-SO_2Me$); C_{1-6} alkenoxy (eg. $-OCH_2CH=CH_2$); C_{1-6} alkylthio (eg. –S-ethyl); $NR^{15}R^{16}$ (eg. $N(Me)_2$); -C_{1-6} alkyl-aryl (eg. benzyl); aryl (eg. phenyl); -CO-aryl (eg. –CO-phenyl) optionally substituted by halogen (eg. chlorine); -CO-heteroaryl (eg. –CO-azetidinyl); -CO-heterocyclyl (eg. –CO-tetrahydropyranyl); $-COOR^{15}$ (eg. COOH, COOMe or COOt-butyl); $-COR^{15}$ (eg. –CO-methyl, -CO-ethyl, -CO-isopropyl, -CO-cyclopropyl, -CO-cyclobutyl, -CO-cyclopentyl or -CO-cyclohexyl); $-CONR^{15}R^{16}$ (eg. $-CONH_2$, -CO-pyrrolidinyl, -CO-morpholinyl, -CO-piperazinyl, -CO-piperidinyl, -CO-thiomorpholinyl) optionally substituted by C_{1-6} alkyl (eg. methyl), halogen (eg. fluorine) or -C_{1-6} alkylC_{1-6} alkoxy (eg. $-CH_2$-OMe); or -C_{1-6} alkyl-CO-aryl (eg. $-CH_2$COphenyl) groups.

More preferably, R^1 is optionally substituted by one or more (eg. 1, 2 or 3): halogen (eg. fluorine); oxo; cyano; $-CONR^{15}R^{16}$ (eg. -CO-pyrrolidinyl) or $-COR^{15}$ (eg. -CO-isopropyl, -CO-cyclopropyl or -CO-cyclobutyl).

Preferably, Z represents a bond, CO or $CONR^{10}$. More preferably, Z represents bond or CO, especially CO.

Preferably, R^{10} represents hydrogen or C_{1-6} alkyl.

Preferably, m is 0 or 2, more preferably 0.

Preferably, n is 0 or 1, more preferably n is 0.

When n represents 1, R^2 is preferably halogen (eg. chlorine, bromine or fluorine), trifluoromethyl, cyano or C_{1-6} alkyl (eg. methyl).

Preferably, r is 0.

When r represents 1 or 2, R^2 is preferably C_{1-6} alkyl (eg. methyl) or two R^4 groups together form a bridged CH_2 group.

Preferably, p is 1.

Preferably, R^3 represents $-(CH_2)_q$-$NR^{11}R^{12}$.

When R^3 represents a group of formula (i), preferably f is 0 or 1, g is 2, h is 1, k is 0 and R^{13} represents hydrogen, optionally substituted C_{1-6} alkyl (eg. ethyl, methylpropyl, isopropyl or methoxyethyl), C_{3-8} cycloalkyl (eg. cyclopropyl, cyclobutyl or cyclopentyl) or -C_{1-6} alkyl-C_{3-8} cycloalkyl (eg. $-CH_2$-cyclopropyl).

When R^3 represents a group of formula (i), more preferably f is 0, g is 2, h is 1, k is 0 and R^{13} represents C_{1-6} alkyl (eg. isopropyl) or C_{3-8} cycloalkyl (eg. cyclopropyl or cyclobutyl).

Preferably, q is 2 or 3, more preferably 3.

Preferably, R^{11} and R^{12} independently represent C_{1-6} alkyl (eg. methyl) or C_{3-8} cycloalkyl (eg. cyclopentyl) or $NR^{11}R^{12}$ represents a heterocyclic group (eg. piperidinyl, pyrrolidinyl, thiomorpholinyl, azepanyl or azocanyl optionally substituted by one or more halogen (eg. fluorine) or C_{1-6} alkyl (eg. methyl or ethyl).

More preferably $NR^{11}R^{12}$ represents pyrrolidinyl, piperidinyl, azepanyl or azocanyl optionally substituted by one or more C_{1-6} alkyl (eg. methyl or ethyl), especially unsubstituted piperidine.

Preferably, -O-R^3 is present at the para position of the phenyl group with respect to the rest of the compound.

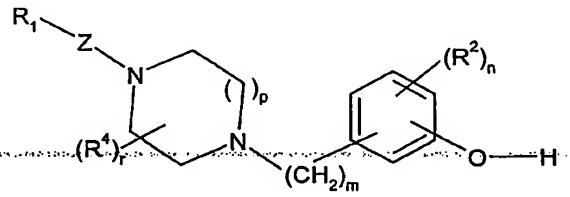
Preferred compounds according to the invention include examples E1-E503 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphuric, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of compounds of formula (I) therefore form an aspect of the invention.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention. For example, when R^3 represents $(CH_2)_qNR^{11}R^{12}$ and $NR^{11}R^{12}$ represents a nitrogen containing heterocyclyl group substituted by one or more C_{1-6} alkyl groups it will be appreciated that the present invention extends to cover diastereomeric and enantiomeric compounds.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

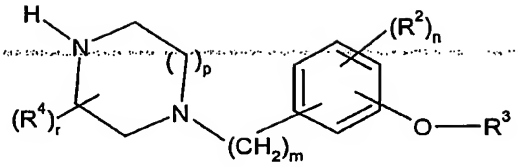
(a) reacting a compound of formula (II)



(II)

wherein R^1, Z, R^4, p, m, r, R^2 and n are as defined above, with a compound of formula $R^{3'}$-L^1, wherein $R^{3'}$ is as defined above for R^3 or a group convertible thereto and L^1 represents a suitable leaving group such as a halogen atom (eg. bromine or chlorine) or an optionally activated hydroxyl group; or

(b) preparing a compound of formula (I) wherein Z represents CO by reacting a compound of formula (III)



(III)

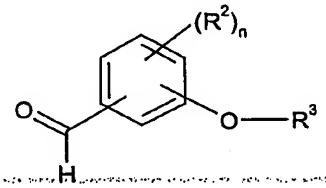
or a protected derivative thereof, wherein R^4, r, p, m, R^2, n and R^3 are as defined above, with a compound of formula R^1-COX, wherein R^1 is as defined above and X represents a suitable leaving group such as an activated hydroxy group, a suitable halogen atom or benzotriazolyl; or

(c) preparing a compound of formula (I) wherein Z represents SO_2 by reacting a compound of formula (III) as defined above with a compound of formula R^1-SO_2Cl, wherein R^1 is as defined above; or

(d) preparing a compound of formula (I) wherein Z represents $NR^{10}CO$ by reacting a compound of formula (III) as defined above with a compound of formula R^1-N=C=O, wherein R^1 is as defined above; or

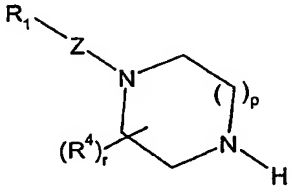
(e) preparing a compound of formula (I) wherein Z represents $CONR^{10}$ by reacting a compound of formula (III) as defined above, sequentially with phosgene in a solvent such as toluene followed by a compound of formula $R^{10}R^1$-NH, in a solvent such as dichloromethane, wherein R^1 and R^{10} are as defined above; or

(f) preparing a compound of formula (I) wherein m represents 1 by reacting a compound of formula (IV)



(IV)

with a compound of formula (XI)



(XI)

or an optionally protected derivative thereof, wherein R^4, r, R^2, n, R^3, R^1, Z and p are as defined above under reducing conditions; or

(g) deprotecting a compound of formula (I) which is protected; and

(h) interconversion to other compounds of formula (I).

When R^3 represents $-(CH_2)_q-NR^{11}R^{12}$, process (a) typically comprises the use of a suitable base, such as potassium carbonate in an appropriate solvent such as 2-butanone optionally in the presence of an activating reagent such as potassium iodide at an appropriate temperature such as reflux.

When a group $R^{3'}$ convertible to R^3 represents, for example, $L^2-(CH_2)_q-$, process (a) typically comprises an alkylation reaction using analogous conditions to those described above.

When R^3 represents a group of formula (i) and L^1 represents an optionally activated hydroxyl group, process (a) typically comprises the use of a phosphine such as triphenylphosphine in a suitable solvent such as tetrahydrofuran, followed by addition of an azodicarboxylate such as diethylazodicarboxylate at a suitable temperature such as room temperature.

Process (b) typically comprises the use of an appropriate solvent such as dichloromethane optionally in the presence of an organic or inorganic base such as potassium carbonate or in the presence of a suitable coupling agent such as 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole.

Processes (c) and (d) typically comprise the use of a suitable solvent such as 2-butanone.

Process (e) typically comprises the use of a suitable base, such as triethylamine.

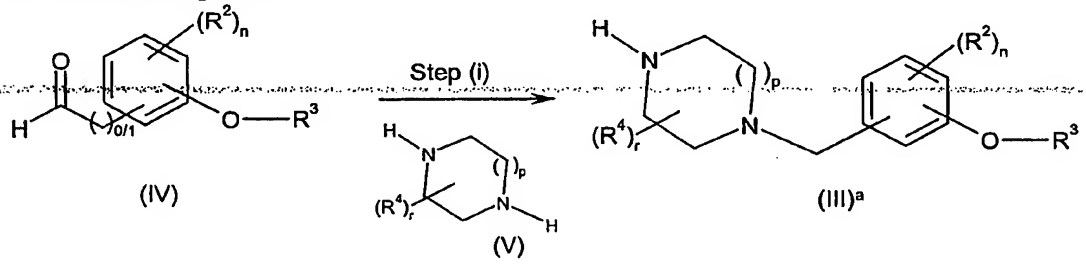
Process (f) comprises the use of reductive conditions (such as treatment with a borohydride eg. sodium triacetoxyborohydride), optionally in the presence of an acid, such as acetic acid, followed by optional deprotection in the event that the compound of formula (XI) is a protected derivative.

In process (g), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-

trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (h) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, compounds of formula (I) wherein R^3 represents a group of formula (i) may be interconverted at the R^{13} position by reaction with an alkyl halide such as 1-chloro-2-methoxyethane in the presence of a base such as potassium carbonate in a suitable solvent such as 2-butanone optionally in the presence of a transfer reagent such as potassium iodide. Such interconversion may also be carried out by reductive amination, for example, with acetone in the presence of a borohydride such as sodium triacetoxyborohydride and optionally an acid such as acetic acid in a suitable solvent such as dichloromethane.

Compounds of formula (II) and (III) wherein m is 1 or 2 may be prepared in accordance with the following scheme:

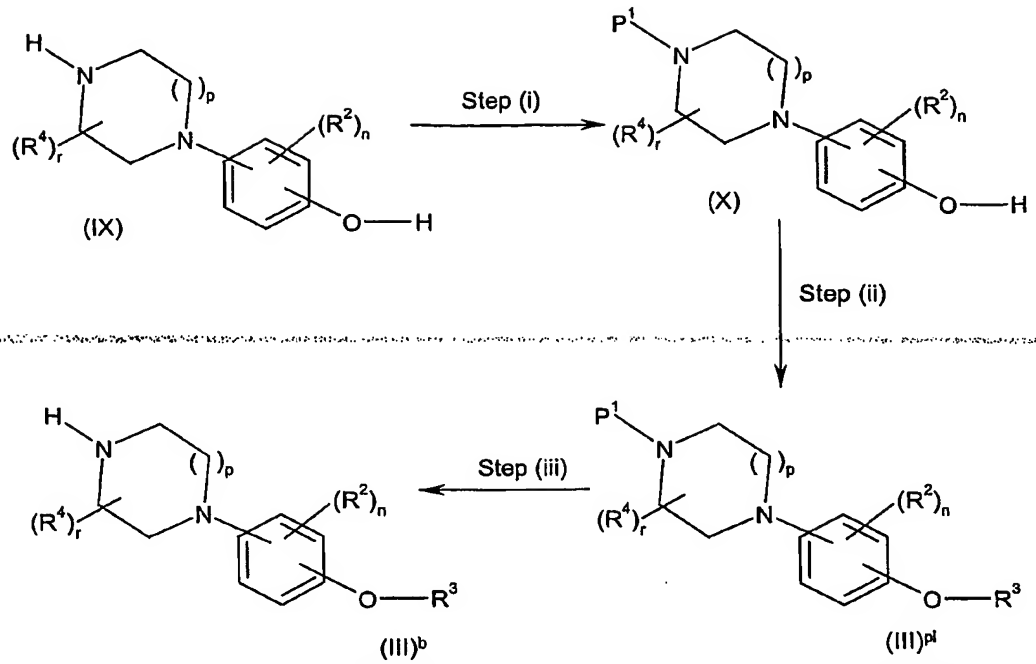


(IV) (V) $(III)^a$

wherein R^4, r, R^2, n, R^3, p are as defined above and the compound of formula (V) may be optionally protected.

Step (i) may be performed in an analogous manner to that described for process (f) above.

Compounds of formula (III) wherein m is 0 may be prepared in accordance with the following scheme:



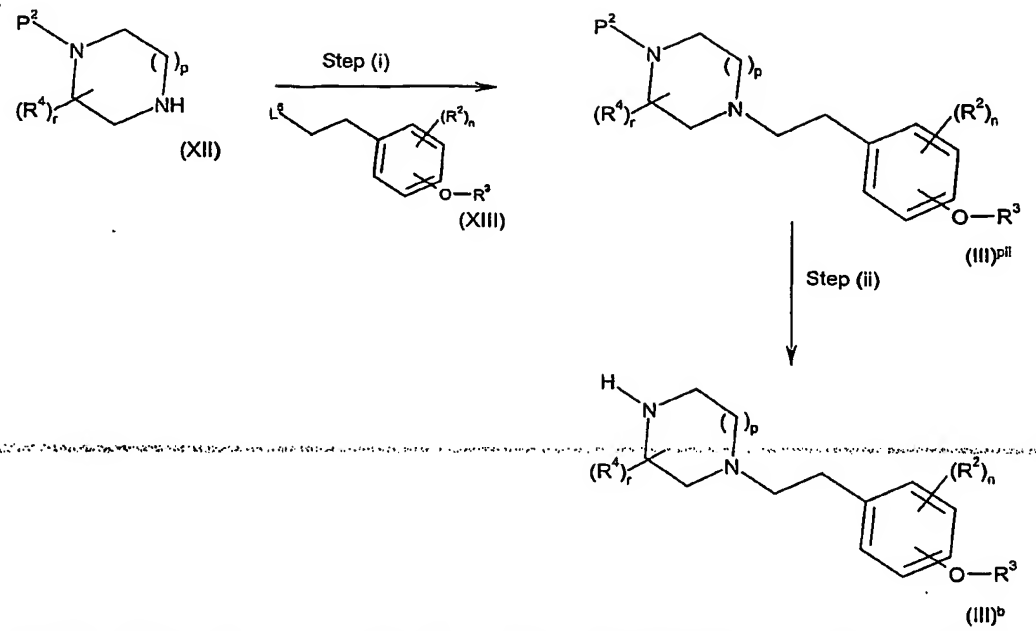
wherein R^4, r, p, R^2, n and R^3 are as defined above and P^1 represents a suitable protecting group (such as Boc).

Step (i) may be performed when P^1 represents Boc by reacting a compound of formula (IX) with di-t-butyl carbonate in the presence of a suitable base (eg. triethylamine) in the presence of a suitable solvent (eg. dichloromethane) at a suitable temperature (eg. room temperature).

Step (ii) may be performed in an analogous manner to the procedures shown below for the preparation of compounds of formula (IV).

Step (iii) typically comprises a deprotection reaction, for example, when P^1 represents Boc, deprotection may typically comprise reaction of a compound of formula $(III)^{pl}$ with hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane.

Compounds of formula (III) wherein m is 2 may be prepared in accordance with the following scheme:



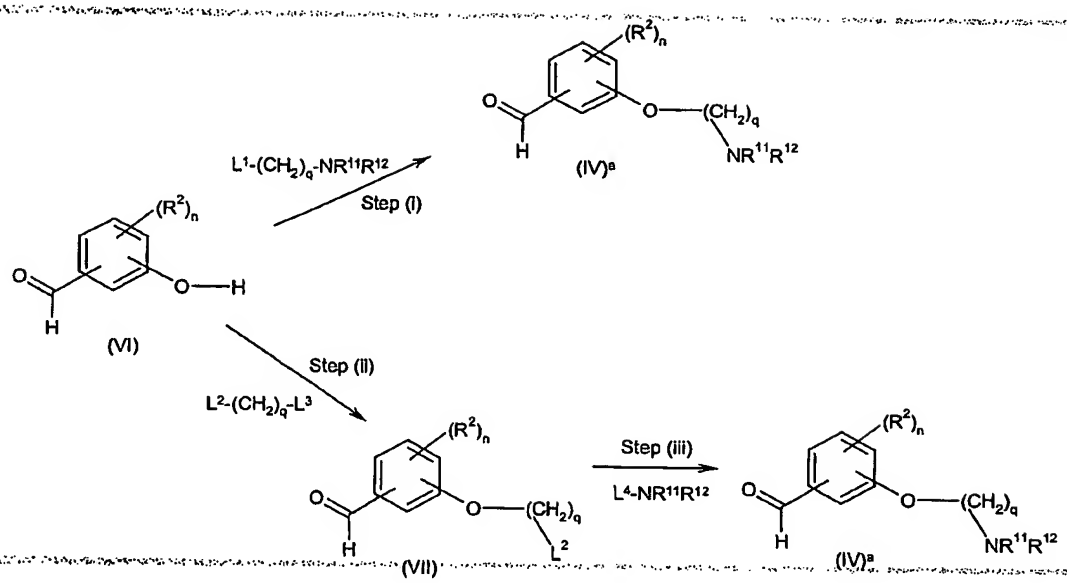
(XII) (XIII) $(III)^{pii}$ $(III)^{b}$

wherein R^2, R^3, R^4, n, p, r are as defined above, P^2 represents a suitable protecting group such as Boc and L^5 represents a suitable leaving group such as a halogen atom (eg. bromine).

Step (i) typically comprises reaction of a compound of formula (XII) with a compound of formula (XIII) in the presence of an inert solvent such as dimethylformamide or acetonitrile.

Step (ii) typically comprises a deprotection reaction, for example, when P^2 represents Boc, deprotection may typically comprise reaction of a compound of formula $(III)^{pii}$ with hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane.

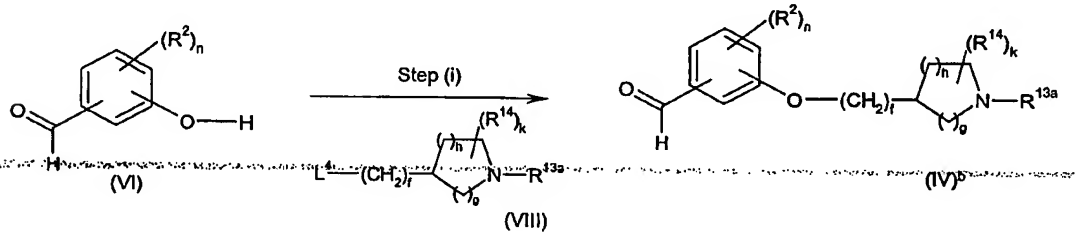
Compounds of formula (IV) wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ may be prepared in accordance with the following scheme:



wherein R^2, n, q, R^{11}, R^{12} are as defined above and L^1, L^2, L^3 and L^4 represent suitable leaving groups (eg. halogen atoms, such as bromine or chlorine).

Steps (i), (ii) and (iii) may be performed using similar conditions to those described for process (a) above.

Compounds of formula (IV) wherein R^3 represents a group of formula (i) as defined above may be prepared in accordance with the following scheme:



wherein R^2, n, f, g, h, k, are as defined above, L^4 represents a suitable leaving group such as a halogen atom or a hydroxyl group and R^{13a} is as defined above for R^{13} or a protecting group such as t-butoxycarbonyl, followed by optional deprotection.

Step (i) may be performed using similar conditions to those described for process (a) above.

Compounds of formula (II) wherein m is 0 may be prepared by a deprotection reaction of a compound of formula (IX) as defined above, followed by an analogous process to

(2002)]. In vivo, H3 receptor agonists inhibit the decrease in nasal airway resistance produced by sympathetic nerve activation [Hey et al, Arzneim-Forsch Drug Res., 48:881-888 (1998)]. Furthermore, H3 receptor antagonists in combination with histamine H1 receptor antagonists reverse the effects of mast cell activation on nasal airway resistance and nasal cavity volume, an index of nasal congestion [McLeod et al, Am. J. Rhinol., 13: 391-399, (1999)]. A combined histamine H1 and H3 receptor antagonist, such as the series described herein, would be effective in the treatment of both the nasal congestion and the sneezing, itching and rhinorrhea associated with both seasonal and perennial allergic rhinitis.

Therefore, examples of disease states in which dual histamine H1 and H3 antagonists have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as asthma (including allergic and non-allergic), allergic rhinitis, sinusitis, bronchitis (including chronic bronchitis), bronchiectasis, chronic obstructive pulmonary disease (COPD) and cystic fibrosis.

Other examples of disease states in which dual histamine H1 and H3 antagonists have potentially beneficial effects include diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure.

Dual histamine H1 and H3 antagonists of the present invention may also be of use in the treatment of sleep/wake disorders, arousal/vigilance disorders, migraine, dementia, mild cognitive impairment (pre-dementia), cognitive dysfunction, Alzheimer's disease, epilepsy, narcolepsy, eating disorders, motion sickness, vertigo, attention deficit hyperactivity disorders, learning disorders, memory retention disorders, schizophrenia, depression, manic disorders, bipolar disorders and diabetes.

Diseases of principal interest for a dual histamine H1 and H3 antagonist include asthma, COPD and inflammatory diseases of the upper respiratory tract involving seasonal and perennial allergic rhinitis, non-allergic rhinitis, and the specific symptoms associated with these diseases including nasal congestion, rhinorrhoea, sneezing, cough and itching (pruritis) of eyes, ears, nose and throat. Other diseases of principal interest include cough, chronic urticaria, allergic conjunctivitis, nasal polyposis, sinusitis, psoriasis, eczema and allergic dermatoses (including urticaria, atopic dermatitis, contact dermatitis, drug rashes and insect bites).

Diseases of principal interest include asthma, COPD, cognitive disorders and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis.

Preferred diseases of principal interest include asthma, cognitive disorders and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis.
Further diseases also of principal interest include inflammatory diseases of the gastrointestinal tract such as inflammatory bowel disease.

Thus the invention also provides a dual histamine H1 and H3 antagonist compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular allergic rhinitis.

Preferred dual histamine H1 and H3 antagonist compounds of formula (I) are those wherein:
R^1 represents aryl (eg. phenyl, naphthyl or tetrahydronaphthyl) or heteroaryl (eg. benzofuranyl, indolyl or quinolinyl);
R^1 is optionally substituted by one or more (eg. 1, 2 or 3): halogen (eg. chlorine, fluorine or bromine); trifluoromethyl; -C_{1-6} alkyl (eg. methyl, ethyl, isopropyl, propyl or t-butyl) optionally substituted by $COOR^{15}$ (eg. COOEt); -C_{1-6} alkoxy (eg. methoxy) optionally substituted by $COOR^{15}$ (eg. COOMe); C_{1-6} alkenyl (eg. ethenyl); $NR^{15}R^{16}$ (eg. $N(Me)_2$); or C_{1-6} alkylthio (eg. –S-ethyl) groups;
Z is a bond or CO;
m is 0 or 2;
n is 0;
r is 0;
p is 1.
R^3 represents -$(CH_2)_q$-$NR^{11}R^{12}$;
q represents 3; and
$NR^{11}R^{12}$ represents pyrrolidinyl, piperidinyl, azepanyl or azocanyl optionally substituted by one or more C_{1-6} alkyl (eg. methyl or ethyl), more preferably piperidinyl substituted by one or two methyl or ethyl groups.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (eg. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, lipoxygenase inhibitors, chemokine antagonists (e.g CCR3, CCR1, CCR2, CXCR1, CXCR2), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or beta adrenergic agents (such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof), or sympathomimetics (e.g pseudoephedrine or oxymetazoline), or other antagonists at the histamine receptor (e.g H4), or cholinesterase inhibitors, or cholinergic antagonists, or antiinfective agents (eg. antibiotics, antivirals).

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, topical, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents,

non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-piperazine-1-carboxylic acid tert -butyl ester (D1)

To a solution of 4-(3-(piperidin-1-yl)propoxy)benzaldehyde (WO 02/12214 A2) (1.90g, 7.68mmol) in dichloromethane (25ml) was added 1-N *tert* butoxy carbonyl piperazine (1.57g, 8.45mmol) followed by acetic acid (1ml), and the reaction stirred for 1 hour at room temperature, then treated with sodium triacetoxy borohydride (2g, 9.61mmol) and stirred for 16 hours at room temperature. The reaction was then diluted with saturated sodium bicarbonate solution and extracted with dichloromethane. The dichloromethane was then washed sequentially with water and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield a residue which was purified using silica gel chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (0.5:4.5:95) to afford the title compound (1.586g, 50%); MS (ES+), m/e 418 $[M+H]^+$.

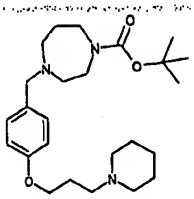
Description 2

1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-piperazine trihydrochloride (D2)

To a solution of 4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazine-1-carboxylic acid tert - butyl ester (D1) (1.576g, 3.76mmol) in a (1:1) mixture of dichloromethane and methanol (20ml) was added a 1M solution of hydrogen chloride in diethyl ether (20ml) and the reaction stirred for 5 hours at room temperature. The solvent was then evaporated *in vacuo* and the resulting residue triturated with diethyl ether to afford the title compound (1.5g, 93%); MS (ES+), m/e 318 $[M+H]^+$.

Description 3

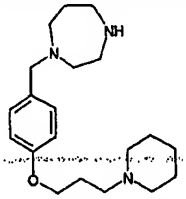
4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (D3)



The title compound (D3) was prepared from [1,4]diazepane-1-carboxylic acid *tert*-butyl ester using the method of Description 1 (D1).
MS(ES+) m/e 432 $[M+H]^+$.

Description 4

1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4)



4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (D3) (2.27g, 5.27mmol) was dissolved in dichloromethane (10ml), treated with trifluoroacetic acid (5ml) and stirred at room temperature under argon for 2 hours. The solvent was removed *in vacuo* and the residue dissolved in methanol and passed down an SCX column (10g) eluting with methanol followed by 0.88 ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (1.57g).
MS(ES+) m/e 332 $[M+H]^+$.

Description 5

4-(4-Formyl-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (D5)

4-Hydroxybenzaldehyde (2.0g, 16.4mmol) was dissolved in tetrahydrofuran (20ml) and treated with 4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (4.1g, 20.5mmol) and

by column chromatography on silica eluting with 4-1 hexane – ethyl acetate to afford the title compound as a colourless viscous oil (3.8 g)
MS (ES+) m/e 355 $[M+H]^+$.

Description 10
4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D10)
A mixture of 4-[4-(3-chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D9) (4.0 g; 11.3 mM), piperidine (2.23 ml; 2 eq), potassium carbonate (3.73 g; 2.4 eq) and potassium iodide (3.74 g; 2 eq) in butan-2-one (100 ml) was heated at reflux for 3 days. The mixture was allowed to cool to room temperature, filtered and evaporated to give the title compound as a pale yellow solid (4.6 g)
MS (ES+) m/e 404 $[M+H]^+$.

Description 11
1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine (D11)
A solution of 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D10) (1.0 g; 2.48 mM) in trifluoroacetic acid (5 ml) was stirred at room temperature for 60 minutes. The resulting mixture was purified on an SCX ion exchange cartridge to afford the title compound as a colourless crystalline solid (0.76 g)
MS (ES+) m/e 304 $[M+H]^+$.

Description 12
4-(3-Hydroxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (D12)
Prepared from 3-piperazin-1-yl-phenol (Chem. Pharm. Bull. 49(10), 1314 (2001)) using the same method described in Description 8 (D8).
MS (ES+) m/e 279 $[M+H]^+$.

Description 13
4-[3-(3-Chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D13)
Prepared from 4-(3-hydroxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (D12) using the same method described in Description 9 (D9).
MS (ES+) m/e 355 $[M+H]^+$.

Description 14
4-[3-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D14)
Prepared from 4-[3-(3-chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D13) using the same method described in Description 10 (D10).
MS (ES+) m/e 404 $[M+H]^+$.

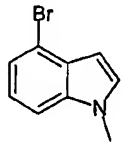
Description 15

1-[3-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine (D15)

Prepared from 4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D14) using the same method described in Description 11 (D11).
MS (ES+) m/e 304 $[M+H]^+$.

Description 16

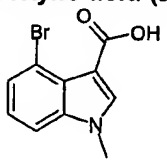
4-Bromo-1-methyl-1*H*-indole (D16)



A solution of 4-bromo-1*H*-indole (6.7 g) in tetrahydrofuran (75 ml) was treated with sodium hydride (1.24 g) and stirred for 0.5 h at room temperature. The resulting suspension was treated with a solution of iodomethane (2.34 ml) in tetrahydrofuran (35 ml) at 0°C and allowed to warm to room temperature over 1h, whilst stirring. The reaction mixture was poured onto water and partitioned between dichloromethane and water. The organic phase was dried over ($MgSO_4$) and concentrated *in vacuo* to afford *the title compound* (7.2 g). TLC Silica (cyclohexane-ethyl acetate [1:1]), Rf = 0.55.

Description 17

4-Bromo-1-methyl-1*H*-indole-3-carboxylic acid (D17)

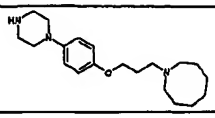
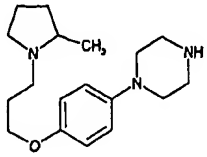
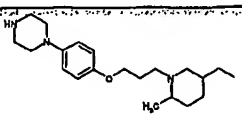
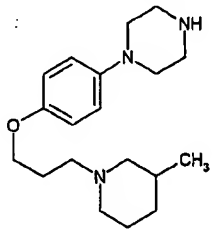
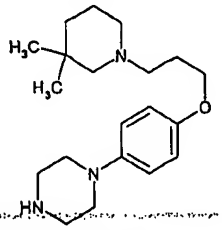
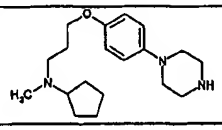


A solution of 4-bromo-1-methyl-1*H*-indole (D16) (7.0 g) in tetrahydrofuran (50 ml) was treated with a solution of trifluoroacetic anhydride (5.65 ml) in tetrahydrofuran (20 ml) at 0°C. The reaction mixture was allowed to warm to room temperature over 6 h, whilst stirring. The reaction mixture was concentrated *in vacuo* and then re-suspended in ethanol (25 ml). The solution was treated with 5N sodium hydroxide solution (50 ml) and heated under reflux for 18 h. The reaction mixture was washed with diethyl ether and the aqueous phase acidified with 5N hydrochloric acid solution. The precipitate was filtered, washed with water and concentrated *in vacuo* to afford *the title compound* (4.88 g). TLC, Silica (cyclohexane-ethyl acetate-acetic acid [3:1:0.1]), Rf = 0.35.

Descriptions 18-23

Descriptions 18-23 were prepared using analogous methods to Example 76b by substituting 2-methylpiperidine with the appropriate amine.

Description	Structure	RT (min)	Mass Ion $(M+H)^+$

18		1.64	332
19		0.65	304
20		1.77	346
21		1.45	318
22		1.57	332
23		1.61	318

Descriptions 24-32

Descriptions 24-32 were prepared by analogous methods to those indicated in the below table:

Description	Name	Prepared analogously to	RT (min)
24	1,1-Dimethylethyl 4-(2-naphthalenyl)-1-piperazinecarboxylate	E229a from known starting materials	3.74
25	1,1-Dimethylethyl 4-(4-quinolinyl)-1-piperazinecarboxylate and 1,1-dimethylethyl 4-(3-quinolinyl)-1-piperazinecarboxylate (1:1)	E229a from known starting materials	2.18 & 3.02

26	1-(2-Naphthalenyl)piperazine	E229b from known starting materials	2.00
27	4-(1-Piperazinyl)quinoline and 3-(1-piperazinyl)quinoline (1:1)	E229b from D25	1.18
28	3-{[4-(2-Naphthalenyl)-1-piperazinyl]methyl}phenol	E229c from D24	2.39
29	3-{[4-(1-Naphthalenyl)-1-piperazinyl]methyl}phenol	E229c from D26	2.41
30	4-{[4-(8-Quinolinyl)-1-piperazinyl]methyl}phenol	E229c from E229b	1.78
31	4-{[4-(4-Quinolinyl)-1-piperazinyl]methyl}phenol and 3-{[4-(3-quinolinyl)-1-piperazinyl]methyl}phenol (1:1)	E229c from D27	1.91
32	4-{[4-(1-Naphthalenyl)-1-piperazinyl]methyl}phenol	E229c from D26	2.46

Descriptions 33-42

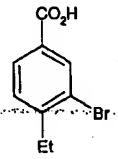
Descriptions 33-42 were prepared by analogous methods to those indicated in the below table:

Description	**Name**	**Prepared analogously to**	**RT (min)**
33	2-Methyl-4-[4-(2-{4-[(phenylmethyl)oxy]phenyl}ethyl)-1-piperazinyl]quinoline	E237a from known starting materials	2.20
34	2-Methyl-4-[4-(2-{3-[(phenylmethyl)oxy]phenyl}ethyl)-1-piperazinyl]quinoline	E237a from known starting materials	2.11
35	1-(1-Naphthalenyl)-4-(2-{4-[(phenylmethyl)oxy]phenyl}ethyl) piperazine	E237a from known starting materials	2.91
36	1-(1-Naphthalenyl)-4-(2-{3-[(phenylmethyl)oxy]phenyl}ethyl) piperazine	E237a from known starting materials	2.82

37	1-Phenyl-4-(2-{4-[(phenylmethyl)oxy]phenyl}ethyl) piperazine	E237a from known starting materials	2.55
38	4-{2-[4-(2-Methyl-4-quinolinyl)-1-piperazinyl]ethyl}phenol	E237b from D33	1.69
39	3-{2-[4-(2-Methyl-4-quinolinyl)-1-piperazinyl]ethyl}phenol	E237b from D34	4.56
40	4-{2-[4-(1-Naphthalenyl)-1-piperazinyl]ethyl}phenol	E237b from D35	2.28
41	3-{2-[4-(1-Naphthalenyl)-1-piperazinyl]ethyl}phenol	E237b from D36	2.32
42	4-[2-(4-Phenyl-1-piperazinyl)ethyl]phenol	E237b from D37	2.02

Description 43

3-Bromo-4-ethyl-benzoic acid (D43)

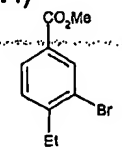


To a mixture of conc. HNO_3 (66 mL), glacial AcOH (300 mL) and water (50 mL), 4-ethyl-benzoic acid (15 g) was added, stirring vigorously, before treating with bromine (5.67 mL). Finally a solution of $AgNO_3$ (16.97 g) in water (50 mL) was added dropwise and the mixture was stirred vigorously for 2 h. The precipitate was collected by filtration, washed well with water, before being extracted with hot, saturated K_2CO_3 solution, and then treated with charcoal. The hot solution was filtered through kieselguhr and the solution was acidified to pH1 using conc. HCl. The resulting white precipitate was collected by filtration and dried in the vacuum oven overnight at 60 °C to afford *the title compound* (19.46 g).

NMR ($CDCl_3$) δ 1.26 (3H, t), 2.83 (2H, q), 7.34 (1H, d), 7.97 (1H, dd), 8.27 (1H, dd)

Description 44

Methyl 3-bromo-4-ethyl-benzoate (D44)

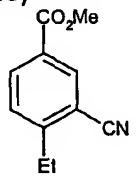


3-Bromo-4-ethyl-benzoic acid (D43) (19.40 g) was dissolved in MeOH (200 mL) and then treated with conc. H_2SO_4 (1 mL). The mixture was heated at reflux overnight, and then concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution, extracting again with EtOAc. The combined

extracts were then washed with brine, dried ($MgSO_4$). The solvent was evaporated *in vacuo* to afford *the title compound* (15.8 g). ^1H NMR ($CDCl_3$) δ 1.24 (3H, t), 2.79 (2H, q), 3.91 (3H, s), 7.29 (1H, d), 7.89 (1H, dd), 8.19 (1H, d).

Description 45

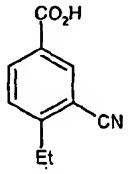
Methyl 3-cyano-4-ethyl-benzoate (D45)



Methyl 3-bromo-4-ethyl-benzoate (D44) (5 g) in NMP (180 mL) was treated with copper (I) cyanide (3.69 g). The mixture was then heated at reflux for 5 h, under argon. After cooling to 20 °C the reaction mixture was diluted with water, then filtered through kieselguhr, washing well with water and EtOAc. The organic layer was washed with water, brine and dried over $MgSO_4$. The solvent was evaporated to dryness *in vacuo* and the residue was purified by chromatography on silica eluting with EtOAc- Hexane (1:9) to give *the title compound* (1.9 g) ^1H NMR ($CDCl_3$) δ 1.33 (3H, t), 2.94 (2H, q), 3.94 (3H, s), 7.43 (1H, d), 8.17 (1H, dd), 8.28 (1H, d).

Description 46

3-Cyano-4-ethyl benzoic acid (D46)



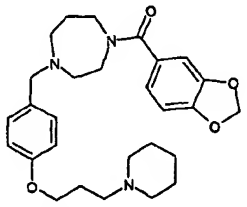
Methyl 3-cyano-4-ethyl-benzoate (D45) (1.92 g) was dissolved in MeOH (50 mL) before adding 1M NaOH solution (15.24 mL) and stirring the resulting mixture overnight at room temperature, under argon. The reaction mixture was diluted with water, and extracted with EtOAc. The aqueous layer was acidified to pH1 using 2M HCl before extracting with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$ and the solvent evaporated to dryness *in vacuo* to afford *the title compound* (1.63 g). ^1H NMR ($CDCl_3$) δ 1.35 (3H, t), 2.97 (2H, q), 7.49 (1H, d), 8.24 (1H, dd), 8.36 (1H, d).

Analysis of the Examples was performed as follows:
LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% formic acid and 0.01M ammonium acetate in water (solvent A) and 0.05% formic acid and 5% water in acetonitrile (solvent B), using the following elution gradient 0.0-7min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5min 0%B at a flow rate of 3 mL/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

methanone (E3)		
1-(3,5-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E4)	3,5-dichlorobenzoic acid	MS (ES+) m/e 491/493 $[M+H]^+$
1-(4-Bromo-3-methyl-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E5)	3-methyl, 4-bromo benzoic acid	MS (ES+) m/e 515/517 $[M+H]^+$
1-(2-Methoxy-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E6)	2-methoxy benzoic acid	MS (ES+) m/e 452 $[M+H]^+$
1-(3,4-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E7)	3,4-dichloro benzoic acid	MS (ES+) m/e 491/493/495 $[M+H]^+$
4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanoyl)-benzonitrile (E8)	4-cyano benzoic acid	MS (ES+) m/e 447 $[M+H]^+$
1-(4-Fluoro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E9)	4-fluoro benzoic acid	MS (ES+) m/e 440 $[M+H]^+$
1-(4-Bromo-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E10)	4-bromo benzoic acid	MS (ES+) m/e 500/502 $[M+H]^+$
1-Benzofuran-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E11)	2-benzofuran carboxylic acid	MS (ES+) m/e 462 $[M+H]^+$

Example 12

1-Benzo[1,3]dioxol-5-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E12)



1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4) (100mg, 0.30mmol) was dissolved in dichloromethane (5ml) and treated sequentially with benzo[1,3]dioxole-5-carboxylic acid (125mg, 0.75mmol), 1,3-dicyclohexylcarbodiimide (155mg, 0.75mmol) and 1-hydroxybenzotriazole hydrate (101mg, 0.75mmol). The mixture was allowed to stir at room temperature under argon for 12 hours, diluted with methanol and passed down an SCX ion exchange column (2g) eluting with methanol followed by 0.880

ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (127mg). MS(ES+) *m/e* 480 [M+H]+.

Examples 13-15

Examples 13-15 (E13-E15) were prepared from Description 4 (D4) using an analogous method to that described in Example 12 (E12) by substituting benzo[1,3]dioxole-5-carboxylic acid for the appropriate acid indicated in the table.

Example	Carboxylic acid	Mass Spectrum
1-Phenyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E13)	Benzoic acid	MS(ES+) m/e 436 $[M+H]^+$
1-Naphthalen-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E14)	Naphthalene-2-carboxylic acid	MS(ES+) m/e 486 $[M+H]^+$
1-(3,5-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E15)	3,5-Dichloro-benzoic acid	MS(ES+) m/e 505 $[M+H]^+$

Examples 16-23

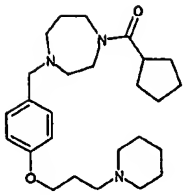
Examples 16-23 (E16-E23) were prepared from Description 4 (D4) using an analogous method to that described in Example 12 (E12) by substituting benzo[1,3]dioxole-5-carboxylic acid for the appropriate acid indicated in the table followed by further purification by column chromatography on silica gel eluting with a mixture of .880 ammonia/methanol/dichloromethane (0.5:4.5:95).

Example	Carboxylic acid	Mass Spectrum
1-(4-Bromo-3-methyl-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E16)	4-Bromo-3-methyl-benzoic acid	MS(ES+) m/e 529 $[M+H]^+$
1-(2-Methoxy-phenyl)-1-{4-[4-(3-piperidin-1-	2-Methoxy-benzoic acid	MS(ES+) m/e 466 $[M+H]^+$

yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E17)		
4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanoyl)-benzonitrile (E18)	4-Cyano-benzoic acid	MS(ES+) m/e 461 $[M+H]^+$
1-(4-Fluoro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E19)	4-Fluoro-benzoic acid	MS(ES+) m/e 454 $[M+H]^+$
1-(4-Bromo-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E20)	4-Bromo-benzoic acid	MS(ES+) m/e 515 $[M+H]^+$
1-Benzofuran-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E21)	Benzofuran-2-carboxylic acid	MS(ES+) m/e 476 $[M+H]^+$
1-(3,4-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E22)	3,4-Dichloro-benzoic acid	MS(ES+) m/e 505 $[M+H]^+$
1-Cyclopropyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E23)	Cyclopropane carboxylic acid	MS(ES+) m/e 400 $[M+H]^+$

Example 24

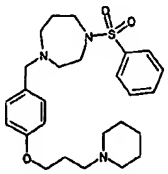
1-Cyclopentyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E24)



1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4) (100mg, 0.30mmol) was dissolved in dichloromethane (5ml), treated with cyclopentyl acid chloride (80mg, 0.60mmol), potassium carbonate (83mg, 0.60mmol) and allowed to stir at room temperature under argon for 12 hours. The reaction mixture was diluted with methanol and passed down an SCX column (2g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (56mg). MS(ES+) *m/e* 428 $[M+H]^+$.

Example 25

1-Benzenesulfonyl-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E25)



1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4) (100mg, 0.30mmol) was dissolved in 2-butanone (5ml), treated with benzene sulfonyl chloride (57mg, 0.32mmol) and allowed to stir at room temperature under argon for 2 hours. The reaction mixture was diluted with methanol and passed down an SCX column (2g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (91mg). MS(ES+) *m/e* 472 $[M+H]^+$.

Examples 26-28

Examples 26-28 (E26-E28) were prepared from Description 4 (D4) using an analogous method to that described in Example 25 (E25) by substituting benzenesulfonyl chloride for the appropriate sulfonyl chloride indicated in the table.

Example	Sulfonyl Chloride	Mass Spectrum
1-(Naphthalene-2-sulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E26)	Naphthalene-2-sulfonyl chloride	MS(ES+) m/e 522 $[M+H]^+$
1-(4-Fluoro-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E27)	4-Fluoro-benzenesulfonyl chloride	MS(ES+) m/e 490 $[M+H]^+$
1-(4-Bromo-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-	4-Bromo-benzenesulfonyl	MS(ES+) m/e 552 $[M+H]^+$

[1,4]diazepane (E28)	chloride	

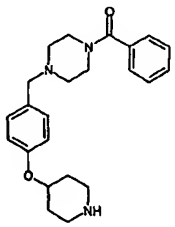
Examples 29-31

Examples 29-31 (E29-E31) were prepared from Description 4 (D4) using an analogous method to that described in Example 25 (E25) by substituting benzenesulfonyl chloride for the appropriate sulfonyl chloride indicated in the table followed by further purification by column chromatography on silica gel eluting with a mixture of .880 ammonia/methanol/dichloromethane (0.5:4.5:95).

Example	Sulfonyl Chloride	Mass Spectrum
1-(3,5-Dichloro-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E29)	3,5-Dichloro-benzenesulfonyl chloride	MS(ES+) m/e 540 $[M+H]^+$
1-(3,4-Dichloro-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E30)	3,4-Dichloro-benzenesulfonyl chloride	MS(ES+) m/e 540 $[M+H]^+$
4-{4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane-1-sulfonyl}-benzonitrile (E31)	4-Cyano-benzenesulfonyl chloride	MS(ES+) m/e 497 $[M+H]^+$

Example 32

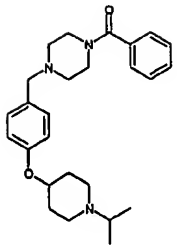
1-Phenyl-1-{4-[4-(piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-methanone (E32)



The title compound (E32) was prepared from 4-{4-[4-(1-phenyl-methanoyl)-piperazin-1-ylmethyl]-phenoxy}-piperidine-1-carboxylic acid tert-butyl ester (D7) using the method described in Description 4 (D4). MS(ES+) m/e 380 $[M+H]^+$.

Example 33

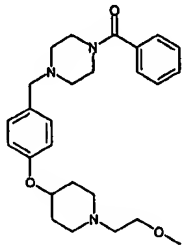
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-1-phenyl-methanone (E33)



The title compound (E33) was prepared from 1-phenyl-1-{4-[4-(piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-methanone (E32) and acetone using the method described in Description 1 (D1). MS(ES+) m/e 422 $[M+H]^+$.

Example 34

1-(4-{4-[1-(2-Methoxy-ethyl)-piperidin-4-yloxy]-benzyl}-piperazin-1-yl)-1-phenyl-methanone (E34)



1-Phenyl-1-{4-[4-(piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-methanone (E32) (150mg, 0.40mmol) was dissolved in 2-butanone and treated with 1-chloro-2-methoxy-ethane (0.08ml, 0.80mmol), potassium carbonate (132mg, 0.96mmol) and potassium iodide (159mg, 0.96mmol). The reaction mixture was heated under reflux for 24 hours. The mixture was allowed to cool to room temperature, acidified by the addition of glacial acetic acid and passed down an SCX ion exchange column (2g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (76mg). MS(ES+) *m/e* 438 $[M+H]^+$.

Examples 35-37

Examples 35-37 (E35-E37) were prepared in accordance with the following general synthesis:

The appropriate acid chloride (1.1 eq) was added to a mixture of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (100 mg; 0.33 mM) and potassium carbonate (55 mg; 1.5 eq) in butan-2-one (2 ml). The resulting mixtures were stirred at room temperature for 3 hours and then purified on SCX ion exchange cartridges to afford the title compounds.

Example	Acid Chloride	Mass Spectrum
1-Cyclopropyl-1-{4-[4-(3-piperidin-	Cyclopropane	MS (ES+) m/e 372

1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E35)	carbonyl chloride	$[M+H]^+$.
1-Phenyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E36)	Benzoyl chloride	MS (ES+) m/e 408 $[M+H]^+$.
1-(3,4-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E37)	3,4-Dichlorobenzoyl chloride	MS (ES+) m/e 477 $[M+H]^+$.

Examples 38-39

Examples 38-39 (E38-E39) were prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same procedure as described in Examples 36 and 37, respectively.

Example	Mass Spectrum
1-Phenyl-1-{4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E38)	MS (ES+) m/e 408 $[M+H]^+$.
1-(3,4-Dichloro-phenyl)-1-{4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E39)	MS (ES+) m/e 477 $[M+H]^+$.

Examples 40-42

Examples 40-42 (E40-E42) were prepared in accordance with the following general synthesis:

The appropriate sulphonyl chloride (1.1 eq) was added to a mixture of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (100 mg; 0.33 mM) and potassium carbonate (55 mg; 1.5 eq) in butan-2-one (2 ml). The resulting mixtures were stirred at room temperature for 3 hours and then purified on SCX ion exchange cartridges to afford the title compounds.

Example	Sulfonyl Chloride	Mass Spectrum
1-Methanesulphonyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E40)	Methane sulfonyl chloride	MS (ES+) m/e 382 $[M+H]^+$.
1-Benzenesulphonyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E41)	Benzene sulfonyl chloride	MS (ES+) m/e 444 $[M+H]^+$.
1-(3,4-Dichloro benzenesulphonyl)-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E42)	3,4-Dichlorobenzene sulfonyl chloride	MS (ES+) m/e 513 $[M+H]^+$.

Examples 43-45

Examples 43-45 (E43-E45) were prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same procedure as described in Examples 40, 41 and 42, respectively.

Example	Mass Spectrum
1-Methanesulphonyl-4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E43)	MS (ES+) m/e 382 $[M+H]^+$.
1-Benzenesulphonyl-4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E44)	MS (ES+) m/e 444 $[M+H]^+$.
1-(3,4-Dichloro benzenesulphonyl)-4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E45)	MS (ES+) m/e 513 $[M+H]^+$.

Examples 46-47

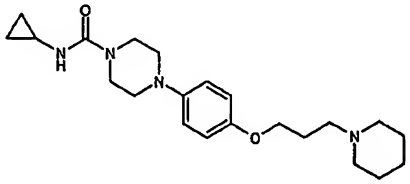
Examples 46-47 (E46-E47) were prepared in accordance with the following general synthesis:

The appropriate isocyanate (1.1 eq) was added to 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (100 mg; 0.33 mM) in butan-2-one (2 ml). The resulting mixtures were stirred at room temperature for 3 hours and then purified on SCX ion exchange cartridges to afford the title compounds.

Example	Isocyanate	Mass Spectrum
4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid phenylamide (E46)	Isocyanatobenzene	MS (ES+) m/e 423 $[M+H]^+$.
4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide (E47)	3,4-Dichloro isocyanato benzene	MS (ES+) m/e 492 $[M+H]^+$.

Example 48

4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid cyclopropylamide (E48)



To a solution of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (150 mg; 0.49 mM) in dry dichloromethane (3 ml) was added drop wise a 20% solution of phosgene in toluene (0.5 ml; ~2 eq) and the resulting mixture stirred for 1 hour. The solvent was

removed by evaporation and the resulting white powder dissolved in dry dichloromethane (4 ml). Triethylamine (0.14 ml: 2 eq) was added followed by cyclopropylamine (0.1 ml; 3 eq) and the mixture stirred for 18 hours. The solvent was removed by evaporation *in vacuo* and the residue purified on a silica column eluting with 3% methanol in dichloromethane to afford the title compound as a white solid (155 mg) MS (ES+) m/e 387 $[M+H]^+$.

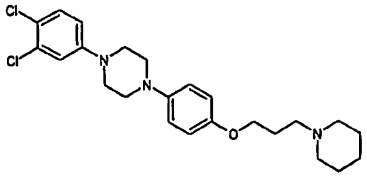
Examples 49-50

Examples 49-50 (E49-E50) were prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same procedure as described in Examples 46 and 47, respectively.

Example	Mass Spectrum
4-[3-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid phenylamide (E49)	MS (ES+) m/e 423 $[M+H]^+$.
4-[3-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide (E50)	MS (ES+) m/e 492 $[M+H]^+$.

Example 51

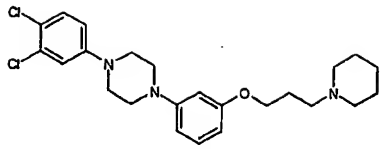
1-(3,4-Dichloro-phenyl)-4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine (E51)



Tris(dibenzylidineacetone) di palladium (0) (5 mol%; 23 mg) was added to a mixture of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (150 mg; 0.49 mmol), 3,4-dichloro bromo benzene (160 mg; 1.2 eq), sodium *tert*-butoxide (71 mg; 1.1 eq) and racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (7.5 mol%; 24 mg) in dry toluene (3ml). The resulting mixture was heated at reflux under argon for 18 hours. The reaction was allowed to cool to room temperature and diluted with ethyl acetate (10 ml). The resulting solids were removed by filtration and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica eluting with 3% methanol in dichloromethane to afford the title compound as a buff solid (45 mg) MS (ES+) m/e 448 $[M+H]^+$.

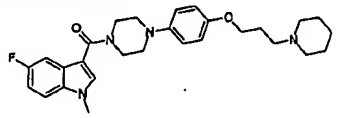
Example 52

1-(3,4-Dichloro-phenyl)-4-[3-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine (E52)



The title compound (E52) was prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same method as described in Example 51 (E51).
MS (ES+) m/e 448 $[M+H]^+$.

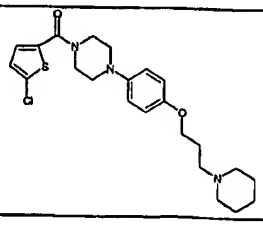
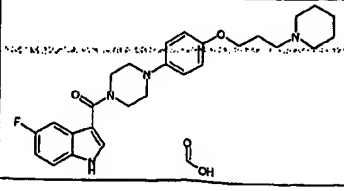
Example 53
5-Fluoro-1-methyl-3-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-1*H*-indole (E53)

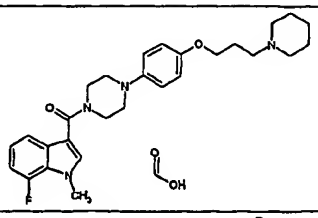
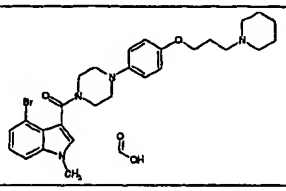
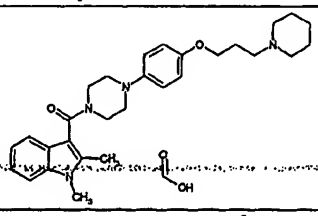
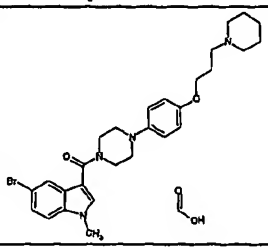
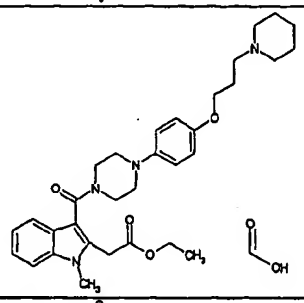
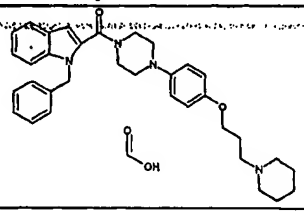


A solution of 5-fluoro-1-methyl-1*H*-indole-3-carboxylic acid [WO 0071537 A1] (35 mg) and 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (D11) (50 mg) in dichloromethane (1ml) was treated with benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (94.4 mg) and heated in a microwave (CEM™ Discover microwave) at 120°C for 5 min. The reaction mixture was concentrated *in vacuo* and purified on a SCX cartridge (2g) eluting with methanol-aqueous ammonia (10:1) followed by mass directed auto preparative HPLC to give *the title compound* (12 mg). LCMS RT = 2.49 min, 478 $(M+H)^+$

Examples 54-61

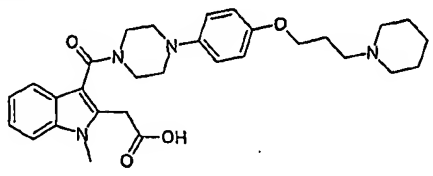
The following compounds were prepared in an analogous manner to the process described for E53 from D11 and a known appropriate acid, with the exception of Example 57 which was prepared from D11 and D17.

Example	Structure	RT (min)	Mass ion $(M+H)^+$
54		2.37	448 450
55		2.26	464

56		2.41	478
57		2.40	539 541
58		2.32	474
59		2.56	539 541
60		2.54	546
61		2.80	536

Example 62

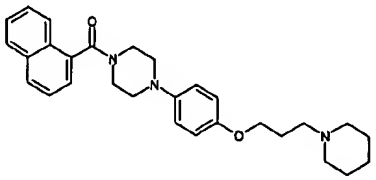
(1-Methyl-3-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-1*H*-indol-2-yl)acetic acid (E62)



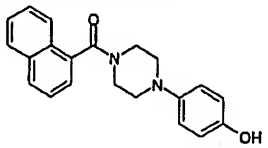
A solution of ethyl (1-methyl-3-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-1*H*-indol-2-yl)acetate (E60) [54 mg] in methanol [6 ml] and water [0.8 ml] was treated with 2N sodium hydroxide [0.46 ml] and was heated under reflux for 2 h. The reaction mixture was quenched with hydrochloric acid [10 ml] at room temperature. The reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate and water. The organic phase was dried and concentrated *in vacuo* to give *the title compound* (20 mg). LCMS RT = 2.35 min, 518 $(M+H)^+$

Example 63

1-(1-Naphthoyl)-4-[4-(3-piperidin-1-ylpropoxy)phenyl]piperazine trifluoroacetate (E63)



E63a: 4-[4-(1-Naphthoyl)piperazin-1-yl]phenol



To a stirring mixture of 4-(1-piperazinyl)phenol (5.54 g) and triethylamine (10.83 ml) in dichloromethane (140 ml) was added dropwise, 1-naphthalenecarbonyl chloride (9.83 ml). The resulting reaction mixture was stirred under a nitrogen atmosphere for 3 h. The mixture was partitioned between dichloromethane and water and the organic phase was washed with saturated brine, dried ($MgSO_4$) and evaporated to dryness. The residue was suspended in 6:4 tetrahydrofuran-methanol (370 ml) and treated with a saturated solution of potassium carbonate in methanol (45 ml). The mixture was stirred at room temperature under a nitrogen atmosphere for 20 h. The solvent was evaporated and the residue was partitioned between dichloromethane and water. The organic phase was washed with saturated brine, dried ($MgSO_4$) and evaporated to give an oil (15.5 g), part of which (14.5 g) was purified by chromatography on a silica SPE bond elut cartridge eluting with 10% -80% ethyl acetate - cyclohexane gradient to give *the title compound* (8.9g). LCMS RT = 2.97 min.

E63b: 1-[4-(3-Chloropropoxy)phenyl]-4-(1-naphthoyl)piperazine

Was prepared from 4-[4-(1-naphthoyl)piperazin-1-yl]phenol (E63a) and 1-bromo-3-chloropropane using the same method described in Description 9 LCMS RT = 3.59 min

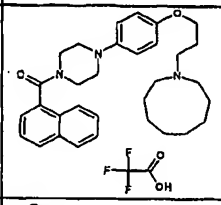
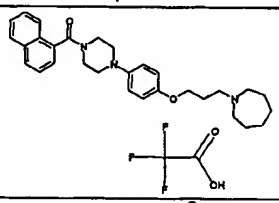
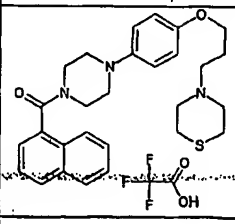
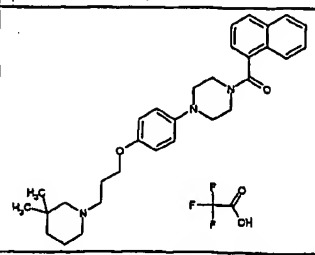
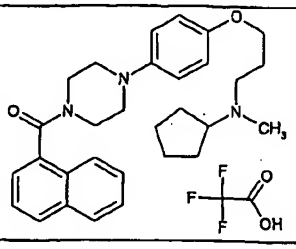
E63c: 1-(1-Naphthoyl)-4-[4-(3-piperidin-1-ylpropoxy)phenyl]piperazine trifluoroacetate

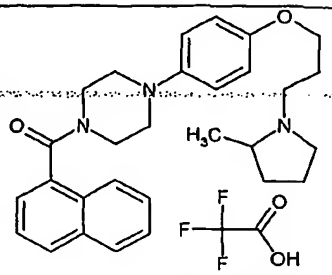
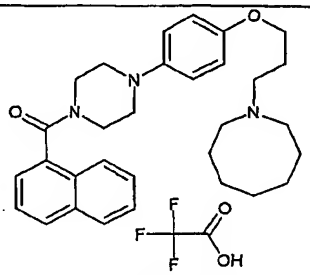
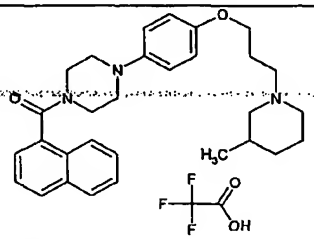
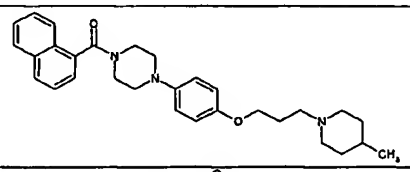
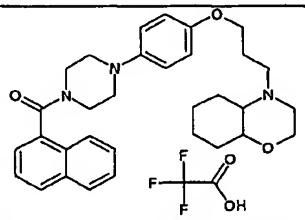
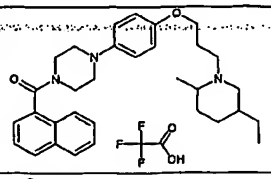
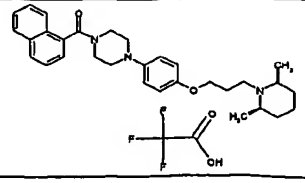
1-[4-(3-Chloropropoxy)phenyl]-4-(1-naphthoyl)piperazine (E63b) (27 mg) piperidine (0.033 ml), potassium carbonate (46 mg), potassium iodide (56 mg)in 2-butanone (2 ml) was heated to reflux for 36 h. The solvent was removed at room temperature by a stream of nitrogen gas. The residue was dissolved in water and dichloromethane. The

organic layer was separated, concentrated and purified by mass directed preparative HPLC to give *the title compound* (23 mg). LCMS RT = 2.15 min, ES+ve m/z 458 $(M+H)^+$.

Examples 64-75

Examples 64-75 were prepared in an array format using the same method described in Example 63c from 1-[4-(3-chloropropoxy)phenyl]-4-(1-naphthoyl)piperazine (0.067 mmol), the appropriate secondary amine (5.0 eq), potassium carbonate (5.0 eq), and potassium iodide (5.0 eq) in 2-butanone (2 ml). The products were purified by mass directed auto-preparative HPLC to provide the compounds as TFA salts.

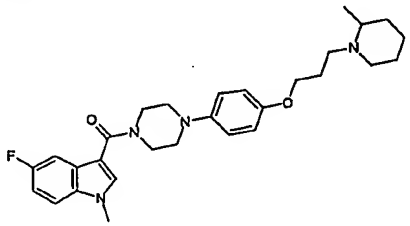
Example	Structure	RT (min)	Mass Ion $(M+H)^+$
64		2.76	500
65		2.63	472
66		2.55	476
67		2.27	486
68		2.66	472

69		2.58	458
70		2.71	485.73
71		2.22	472
72		2.22	472
73		2.26	514
74		2.35	500
75		2.24	486

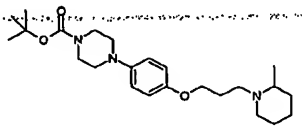
Example 76

00R **5-Fluoro-1-methyl-3-[(4-{4-[3-(2-methylpiperidin-1-yl)propoxy]phenyl}piperazin-1-**

Example 76
5-Fluoro-1-methyl-3-[(4-{4-[3-(2-methylpiperidin-1-yl)propoxy]phenyl}piperazin-1-yl)carbonyl]-1*H*-indole (E76)

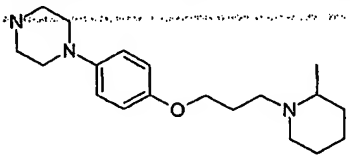


E76a: 1,1-Dimethylethyl 4-(4-{[3-(2-methyl-1-piperidinyl)propyl]oxy}phenyl)-1-piperazinecarboxylate



1,1-Dimethylethyl 4-{4-[(3-chloropropyl)oxy]phenyl}-1-piperazinecarboxylate (D9) (1.6g), was dissolved in 2-butanone (10ml). Potassium carbonate (1.38g) and a catalytic amount of potassium iodide were added, followed by 2-methylpiperidine (0.99g). The mixture was heated at reflux for 72 h under nitrogen. The reaction mixture was diluted with water and extracted with dichloromethane. The organic phases were separated using a hydrophobic frit, combined and evaporated *in vacuo*. The residue was purified on a 100g silica SPE bond elut cartridge, eluting with a gradient of 0% to 20% [0.880 ammonia-methanol (1:9)]-dichloromethane mixtures, to give *the title compound* (1.66g). LCMS RT= 2.48min.

E76b: 1-(4-{[3-(2-Methyl-1-piperidinyl)propyl]oxy}phenyl)piperazine



1,1-Dimethylethyl 4-(4-{[3-(2-methyl-1-piperidinyl) propyl]oxy}phenyl)-1-piperazinecarboxylate (E76a) (1.66 g) was dissolved in dry dichloromethane (25 ml) and stirred under nitrogen. 50% Trifluoroacetic acid in dichloromethane (5ml) was added, and the mixture was stirred at room temperature for 4 h. Saturated sodium bicarbonate solution was then added and the mixture was extracted with dichloromethane. The organic phase was separated using a hydrophobic frit, and evaporated *in vacuo,* however, most of the product was in the aqueous phase. The product was removed from the aqueous phase using an OASIS cartridge, washing with water and eluting with methanol, and further purified using an aminopropyl bond elut cartridge, eluting with dichloromethane and then SCX cartridge, eluting with 50% [0.880 ammonia-methanol

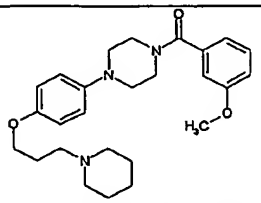
(1:9)]-dichloromethane to give *the title compound* (0.94 g). LCMS RT= 1.01min, ES+ve m/z = 318 $(M+H)^+$

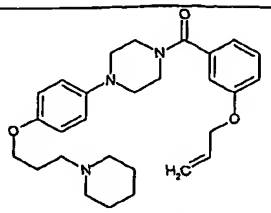
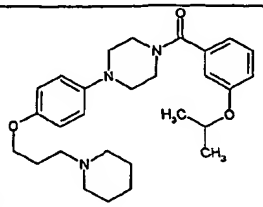
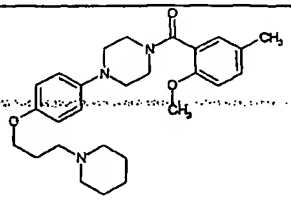
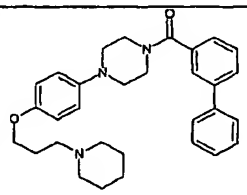
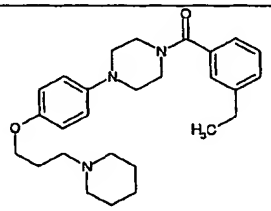
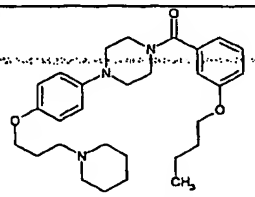
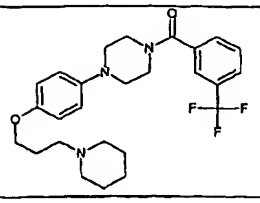
E76c: 5-Fluoro-1-methyl-3-[(4-{4-[3-(2-methylpiperidin-1-yl)propoxy]phenyl}piperazin-1-yl)carbonyl]-1*H*-indole

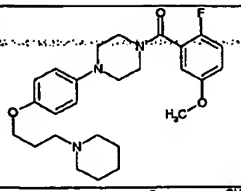
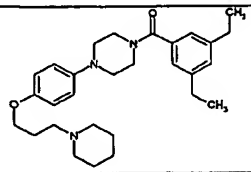
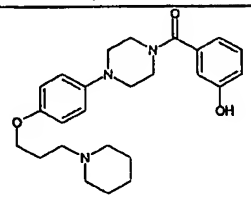
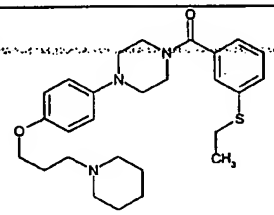
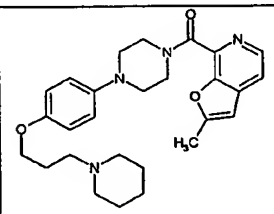
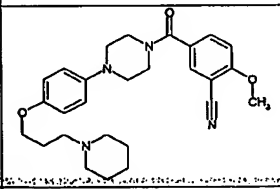
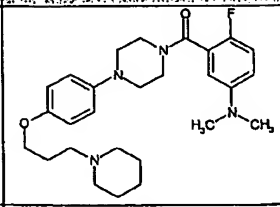
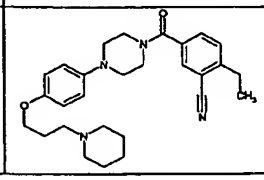
A solution of 5-fluoro-1-methyl-1*H*-indole-3-carboxylic acid (19.3 mg) and *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) (56mg) in DMF (1 ml) and diisopropylethylamine (0.035 ml) was stirred for 10 min before 1-{4-[3-(2-methylpiperidin-1-yl)propoxy]phenyl}piperazine (E76b) (21.3 mg) in DMF (0.5 ml) was added. The mixture was stirred for 18 h and then concentrated under reduced pressure. The residue was purified by SPE ion exchange chromatography on an SCX-2 cartridge (1g). The cartridge was washed with methanol (3 ml) and the product eluted with 2M ammonia in methanol (2.5 ml), to give *the title compound* (15 mg) LCMS RT = 2.42 min, ES+ve m/z 493 $(M+H)^+$.

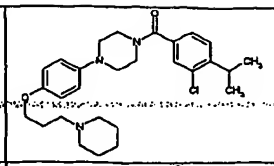
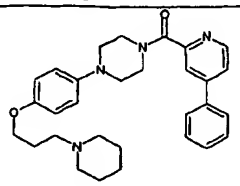
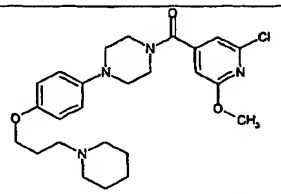
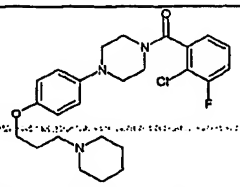
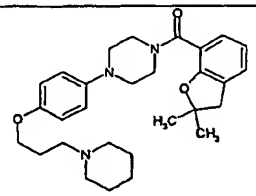
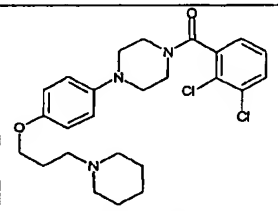
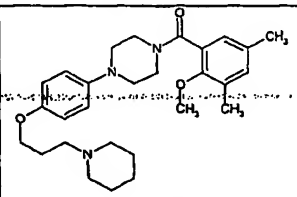
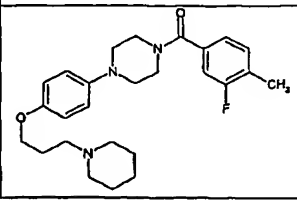
Examples 77-224

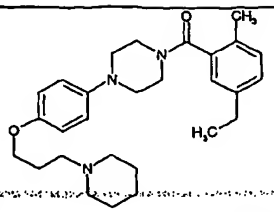
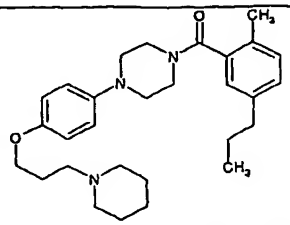
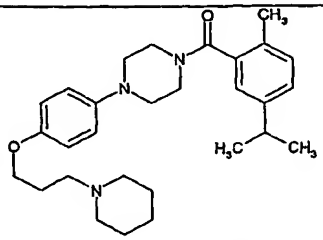
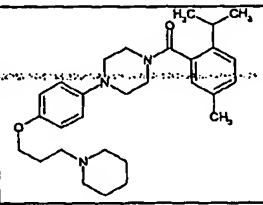
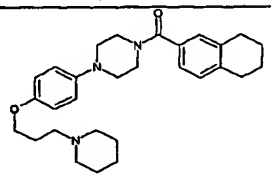
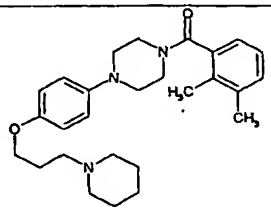
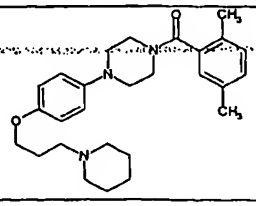
Examples 77 to 224 were prepared in an array format in vials using a solution of the appropriate carboxylic acid (0.1 mmol) in DMF (0.5 ml) and a solution of *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) (0.15mmol) in DMF (0.5 ml) and diisopropylethylamine (0.2 mmol). Each vial was shaken manually and stood for 10 min, before a solution of the appropriate piperazine (selected from D18-D23 or D46 in the case of Example 99) (0.067 mmol) in DMF (0.5 ml) was added to each reaction mixture. The vials were left to stand overnight for approximately 18 h at room temperature. Each solution was then added to the top of a preconditioned SCX-2 SPE cartridge (1g). The cartridge was washed with methanol (3 ml) and the product eluted with 2M ammonia in methanol (2.5 ml), into pre-weighed vials. The solutions were evaporated to dryness on the genevac to provide the products (Examples 77-222). Examples 151, 154, 162-171 and 206-222 were further purified by mass directed auto-preparative HPLC to provide the products as trifluoroacetate salts.

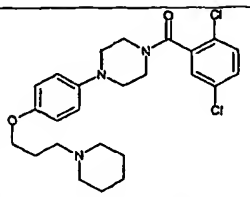
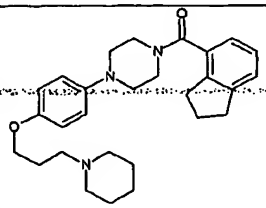
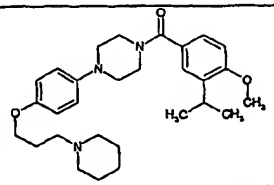
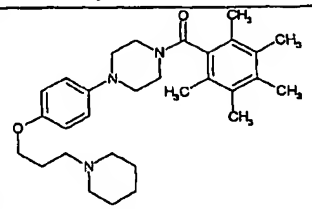
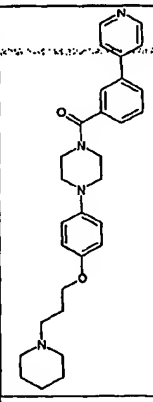
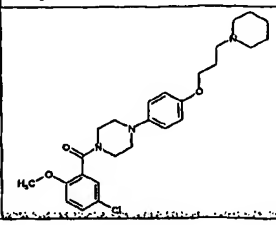
Example	Structure	RT (min)	Mass ion $(M+H)^+$
77		2.36	438

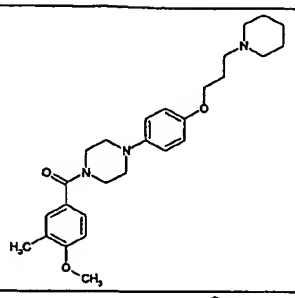
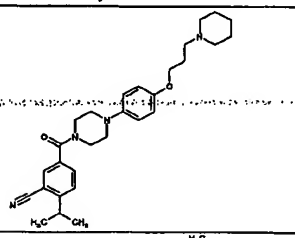
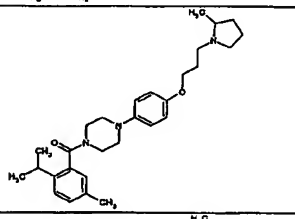
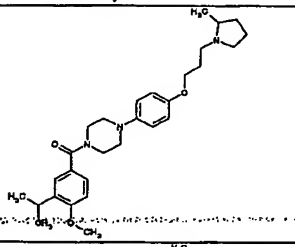
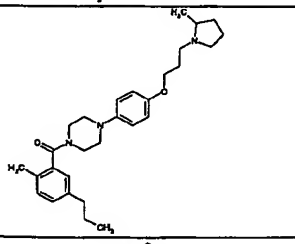
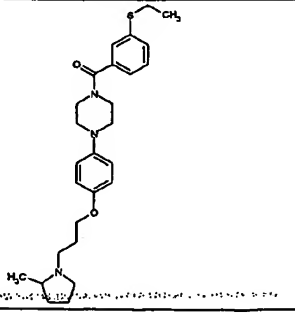
78		2.52	464
79		2.55	466
80		2.44	452
81		2.74	484
82		2.52	436
83		2.74	480
84		2.58	476

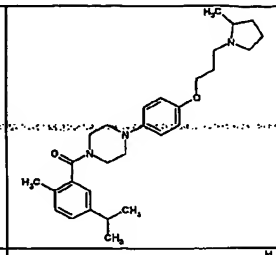
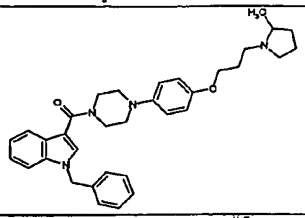
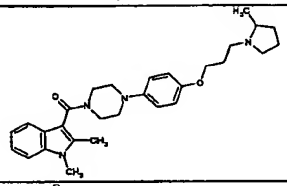
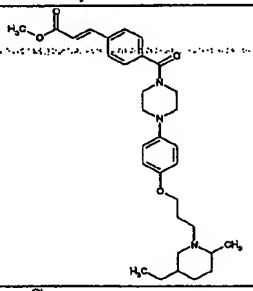
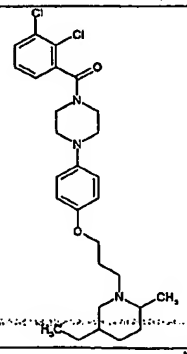
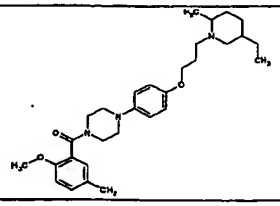
92		2.23	456
93		2.76	464
94		2.24	424
95		2.16	468
96		1.87	463
97		1.96	463
98		1.85	467
99		2.11	461

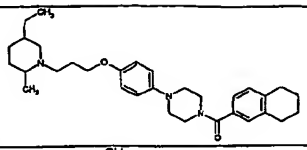
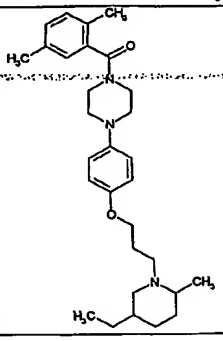
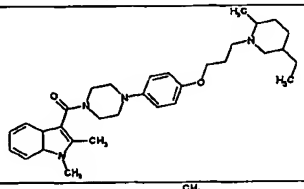
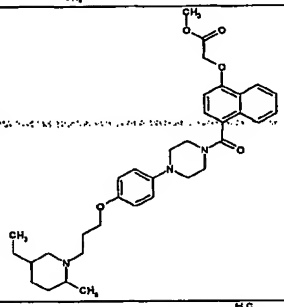
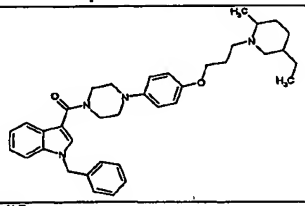
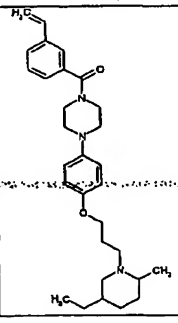
100		2.37	484
101		2.11	485
102		2.05	473 475
103		2.07	460 462
104		2.07	478
105		2.18	476 478
106		2.13	466
107		2.05	440

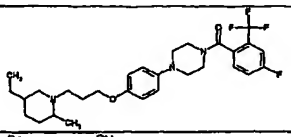
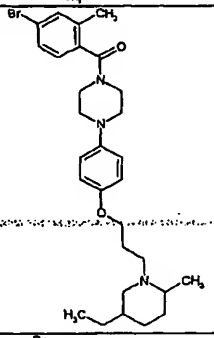
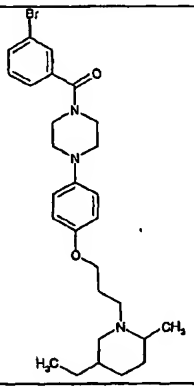
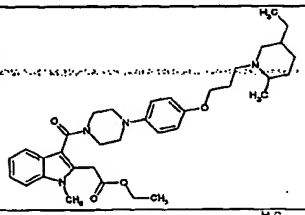
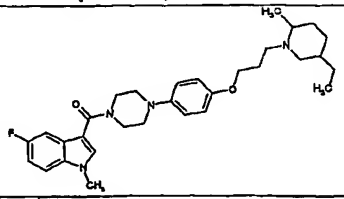
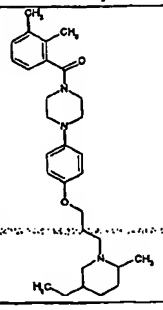
108		2.20	450
109		2.31	464
110		2.31	464
111		2.29	464
112		2.22	462
113		2.07	436
114		2.07	436

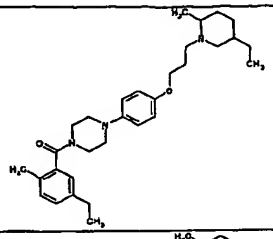
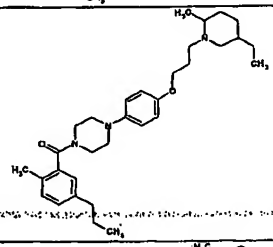
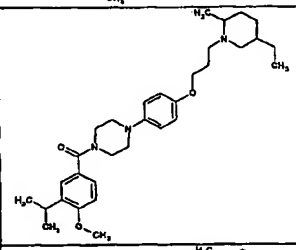
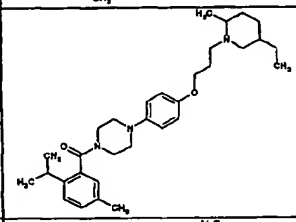
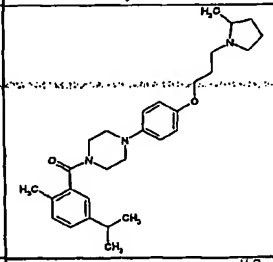
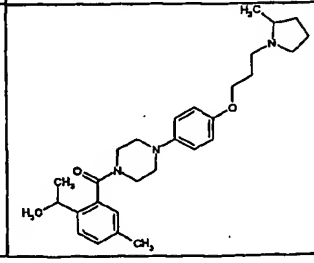
115		2.12	476 478
116		2.13	448
117		2.26	480
118		2.29	478
119		2.15	485
120		2.52	472

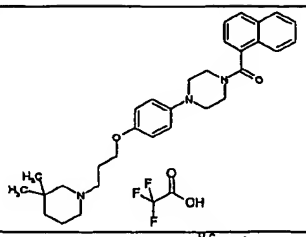
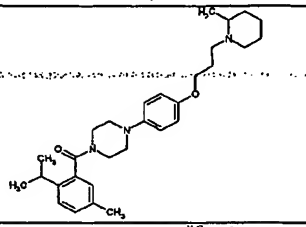
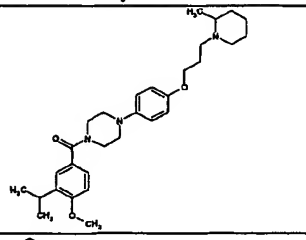
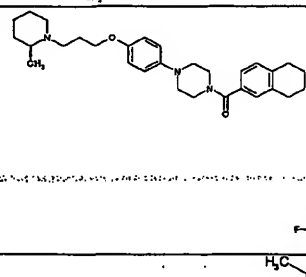
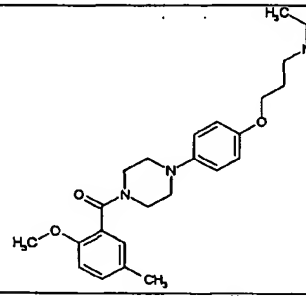
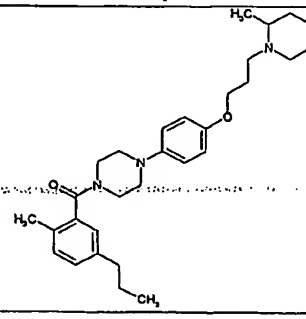
121		2.52	452
122		2.63	475
123		2.53	464
124		2.53	480
125		2.60	464
126		2.47	468

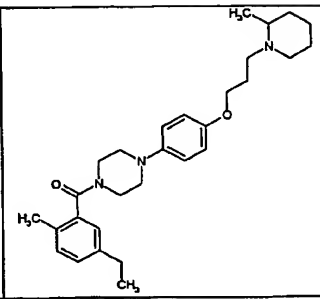
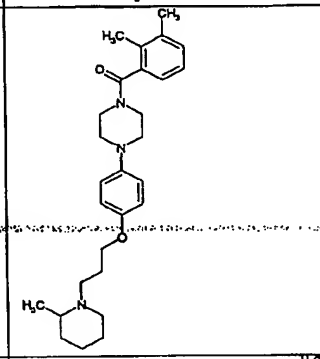
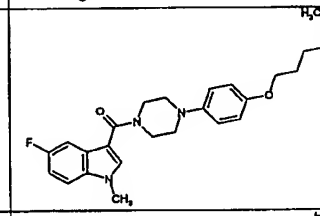
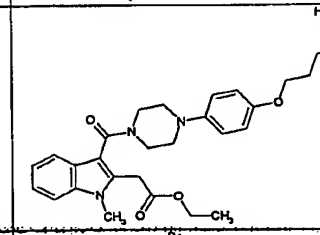
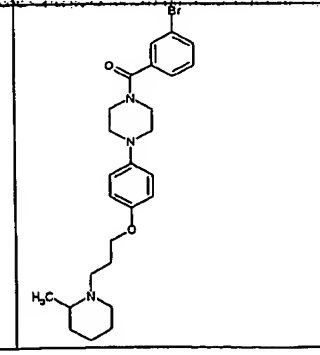
127		2.59	464
128		2.61	537
129		2.37	475
130		2.58	534
131		2.66	518 520
132		2.54	494

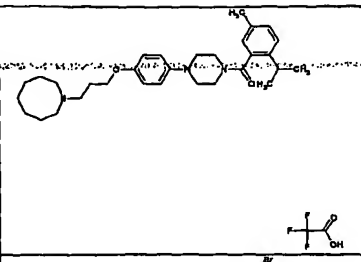
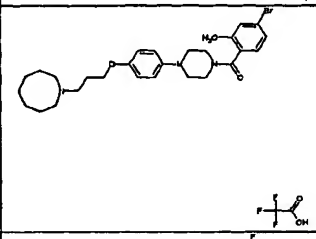
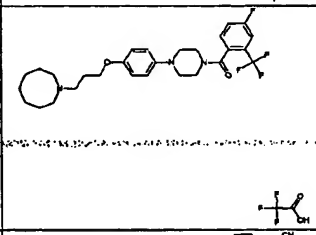
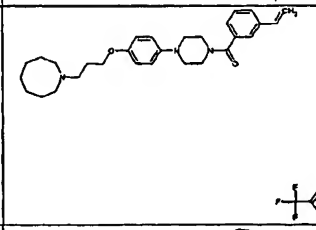
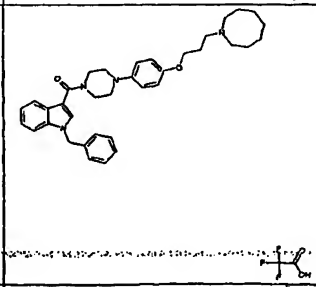
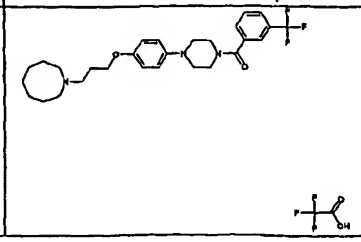
133		2.76	504
134		2.60	478
135		2.60	517
136		2.65	588
137		2.83	579
138		2.60	476

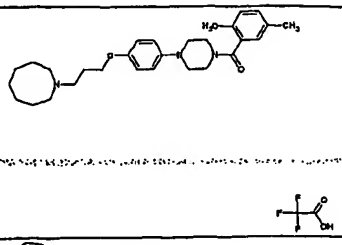
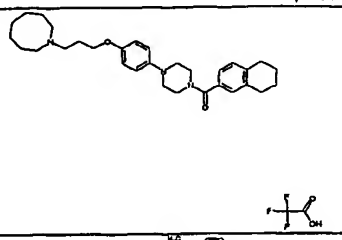
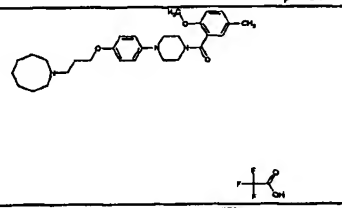
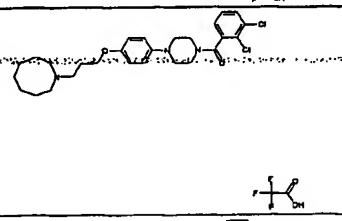
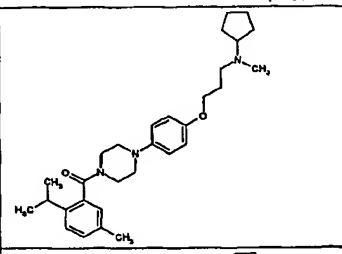
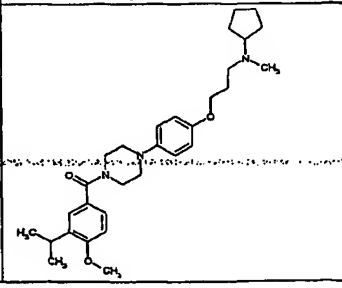
139		2.63	536
140		2.69	542 544
141		2.62	528 530
142		2.68	589
143		2.61	521
144		2.58	478

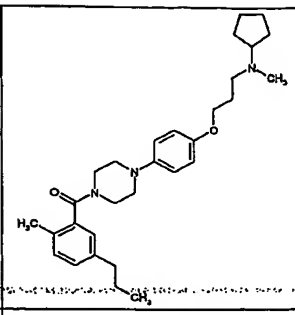
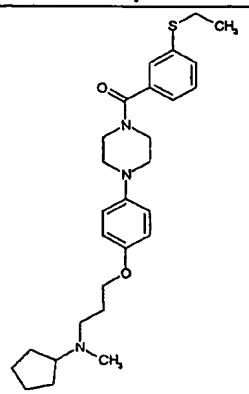
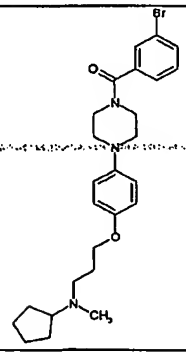
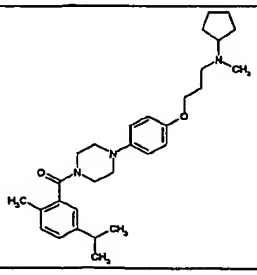
145		2.70	492
146		2.81	506
147		2.77	522
148		2.77	506
149		2.59	464
150		2.57	464

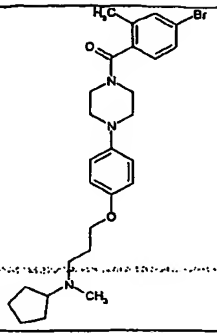
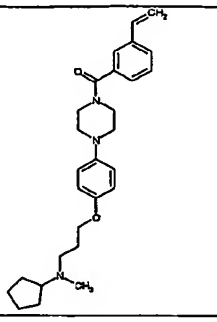
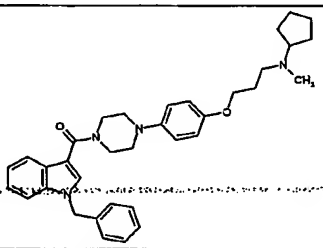
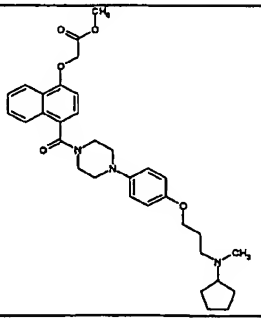
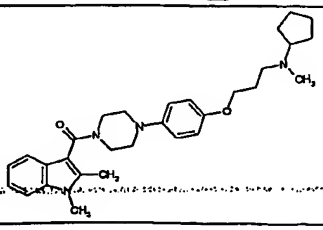
151		2.27	486
152		2.60	478
153		2.63	494
154		2.36	466
155		2.36	466
156		2.65	478

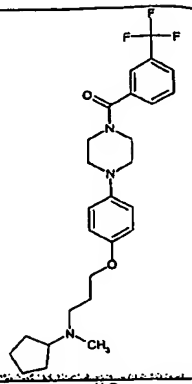
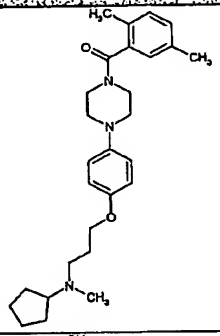
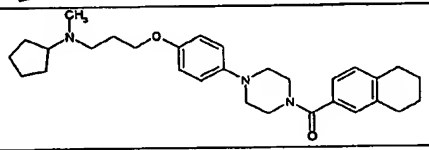
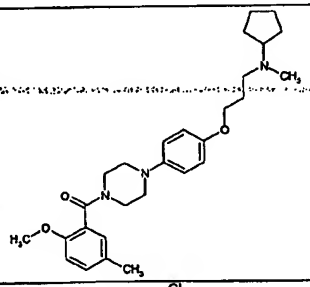
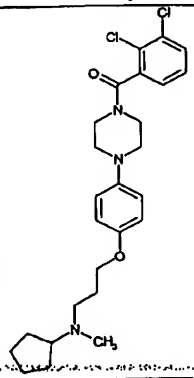
157		2.54	464
158		2.40	450
159		2.42	493
160		2.42	561
161		2.51	500 502

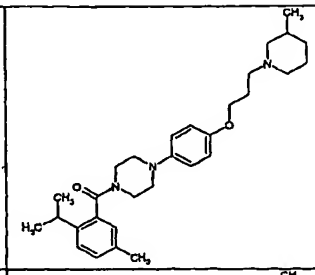
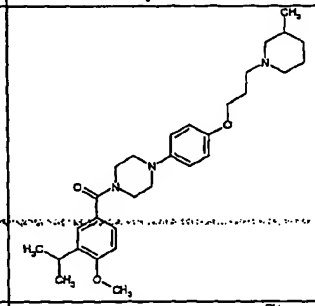
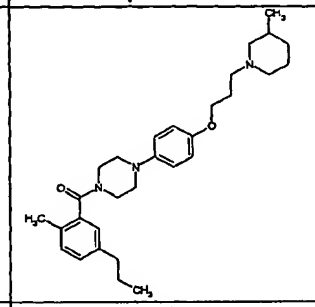
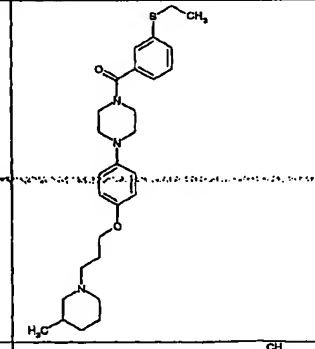
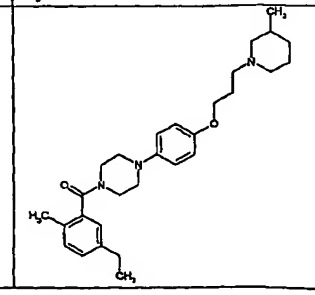
162		2.66	492
163		2.60	528 530
164		2.54	522
165		2.51	462
166		2.76	565
167		2.55	504

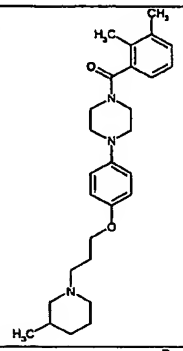
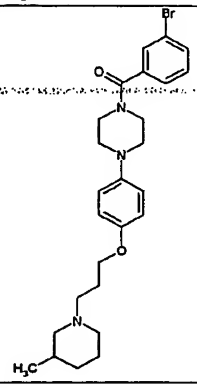
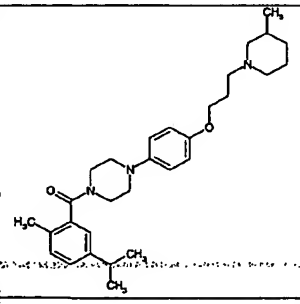
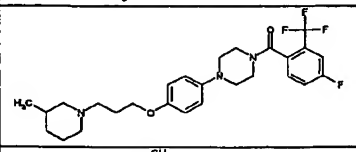
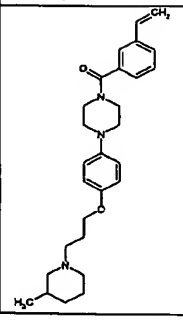
168		2.51	464
169		2.67	490
170		2.45	480
171		2.57	504 506
172		2.63	478
173		2.65	494

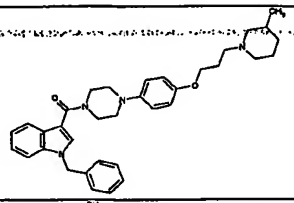
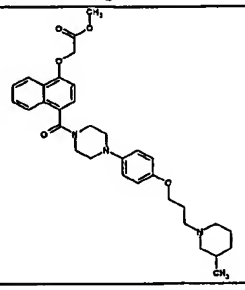
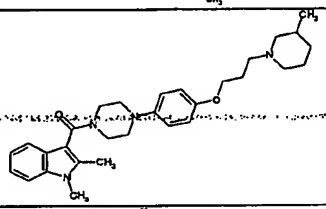
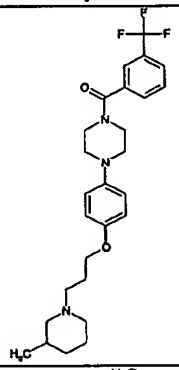
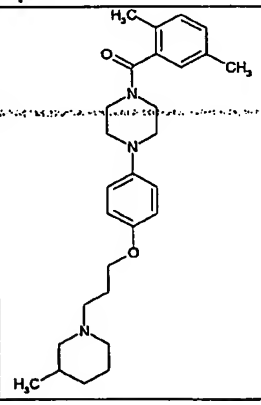
174		2.69	478
175		2.56	482
176		2.49	500 502
177		2.66	478

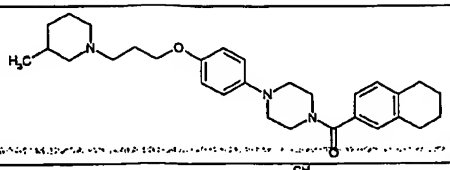
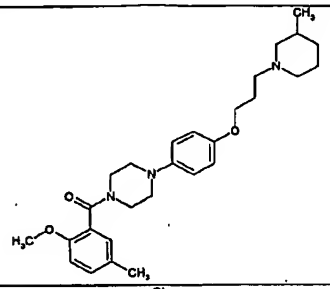
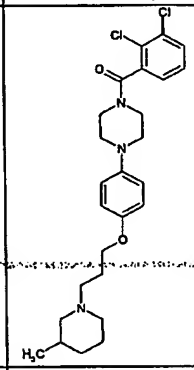
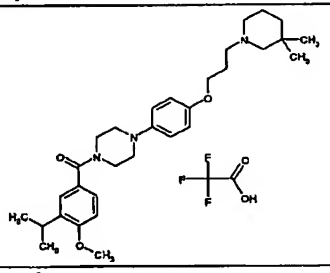
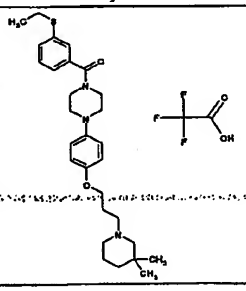
178		2.55	514 516
179		2.47	448
180		2.72	551
181		2.52	560
182		2.47	489

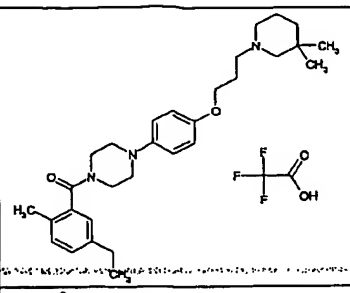
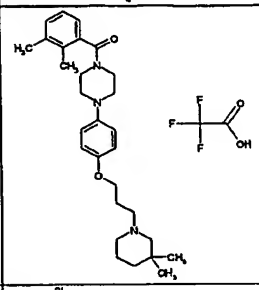
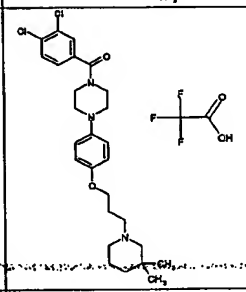
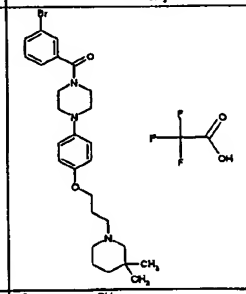
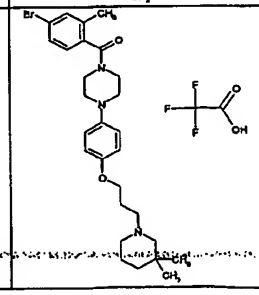
183		2.54	490
184		2.47	450
185		2.60	476
186		2.39	466
187		2.53	491

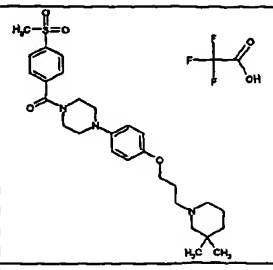
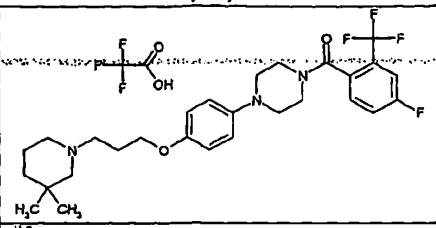
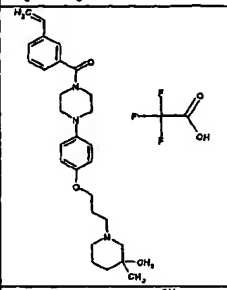
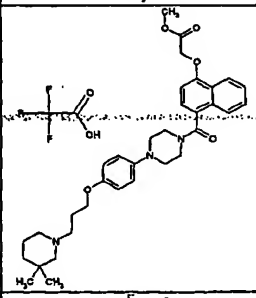
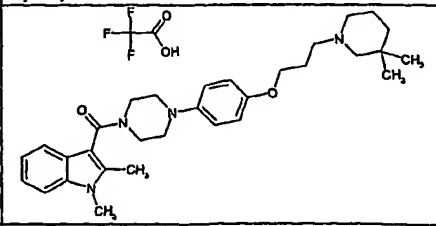
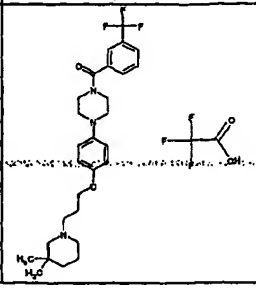
188		2.63	478
189		2.64	494
190		2.68	478
191		2.58	482
192		2.55	464

193		2.44	450
194		2.47	500 502
195		2.66	478
196		2.44	508
197		2.44	448

198		2.71	551
199		2.52	560
200		2.46	489
201		2.50	490
202		2.46	450

203		2.62	476
204		2.39	466
205		2.52	490 492
206		2.40	508
207		2.37	496

208		2.35	478
209		2.27	464
210		2.37	504 506
211		2.26	514 516
212		2.34	528 530

213		2.00	514
214		2.28	522
215		2.26	462
216		2.57	574
217		2.30	503
218		2.30	504